

# A Retrospective Case Control Study to Evaluate the Frequency of Pap Smear Abnormalities among HIV-seropositive and HIV-seronegative Women

Radha Bai Prabhu Thangappah<sup>1</sup>, Gayathri Sureshbabu<sup>2</sup>, Sri Varshitha Desu<sup>3</sup>, Vidhya Subramanian<sup>4</sup>

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## ABSTRACT

**Introduction:** WHO has recommended global action to eliminate cervical cancer by the 21st century. HIV-infected women are at increased risk of acquiring HPV infection, progressing to pre-invasive, and invasive cervical cancers.

**Objectives:** The objective was to assess the frequency of and the risk factors for pap smears abnormalities in HIV-seropositive and HIV-seronegative women.

**Materials and methods:** This retrospective case control study conducted in a Medical College Hospital from January 2016 to December 2019 included case records of 330 married women aged more than 19 years. About 270 participants were eligible for controls and 60 for cases. Demographic details, CD4 count, and pap smear findings were noted, and statistical analysis was carried out.

**Results:** Pap smear abnormalities were noted in 13.3% of HIV-infected women and 1.85% of HIV-negative women. The preponderance of inflammatory smear was 61.7% among seropositive women and 47% among seronegative women. The mean CD4 count among HIV-positive women was  $534.34 \pm 242.24$  and in 64.14%, the CD4 count was  $>400$ . No statistically significant association between the abnormal pap smear results and the age of the individual, parity, and age at first intercourse was noted.

**Conclusion:** Abnormal cervical cytology was seven times higher in HIV-infected women when compared with HIV-negative women and immunosuppression may be the predominant risk factor leading to cytological abnormalities in HIV-infected women. HIV-positive women showing inflammatory smears need further evaluation.

**Keywords:** Cervical carcinoma, Human immunodeficiency virus, Pap smear abnormalities, Risk factors.

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## INTRODUCTION

The recent report by the WHO on cervical cancer has shown that 604,000 new cases of cervical cancers were reported in 2020 and there were 342,000 deaths related to the disease.<sup>1</sup> About 84% of the reported cervical cancers were reported from lower-resource countries, with China and India together accounting for 35% of the global burden.<sup>2</sup> India has an enormous burden of cervical carcinoma with 122,844 women diagnosed with cervical cancer and 67,477 die of the disease every year. The incidence of cervical cancer is also high in India at 22/100,000 women, compared with 19.2 in Bangladesh, 13 in Sri Lanka, and 2.8 in Iran.<sup>3</sup> The WHO has set a target to reduce the global incidence of cervical cancer to 4 per 100,000 women in the 21st century. In order to achieve this goal, the WHO has recommended vaccinating 90% of all girls by the age of 15 years, screening 70% of women twice in their life time and treating 90% of the detected pre-cancerous cervical lesions.<sup>4</sup> Cervical cancer is caused by the persistent infection with a high-risk oncogenic human papillomavirus (HPV). It has been shown that women who are infected with the human immunodeficiency virus (HIV) are at increased risk of acquiring HPV infection, progressing to pre-invasive and invasive cervical cancers.<sup>5-7</sup> Cervical cancer is shown to be eight times more common in HIV-seropositive women than the HIV-seronegative women and they also develop invasive cervical cancer 10 years earlier.<sup>8</sup> The National AIDS Control Organization (NACO) estimated that 2.14 million people were reported with HIV/AIDS in India in 2017.<sup>9</sup> India HIV Estimation 2019 report has shown that the prevalence of HIV is declining in India.<sup>10</sup>

<sup>1-4</sup>Department of Obstetrics and Gynaecology, Sri Muthukumaran Medical College Hospital and Research Institute, Chennai, Tamil Nadu, India

**Corresponding Author:** Radha Bai Prabhu Thangappah, Department of Obstetrics and Gynaecology, Sri Muthukumaran Medical College Hospital and Research Institute, Chennai, Tamil Nadu, India, Phone: +91 9444051124, e-mail: radhaprabhu54@gmail.com

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Studies have shown that women who are infected with HIV are at increased risk of acquiring high-risk HPV (HR-HPV), reduced clearance of HPV, and increased risk of pre-cancerous and invasive cervical cancer when compared with HIV-negative women.<sup>11-13</sup> In recent years, it has been shown that this risk is reduced probably due to the use of effective antiretroviral therapy (eART) and by implementing cervical cancer screening.<sup>14</sup>

## AIMS AND OBJECTIVES

The objectives of this study were to assess the prevalence and the risk factors for pap smear abnormalities among HIV-positive and

HIV-negative women and to study the association of pap smear abnormalities with immune status (CD4 count) of the individual and antiretroviral therapy among HIV-positive women.

## MATERIALS AND METHODS

This is a retrospective study conducted by the Department of Obstetrics and Gynecology in a Medical College Hospital at Chennai. Permission from the Institutional review board was obtained to conduct this study. The material for the study was collected from the case records of the gynecological patients for the period from January 2016 to December 2019. The study data included case records of married women who were more than 19 years of age. Women who have never had sexual contact, women with known pre-invasive and invasive cervical cancers, and hysterectomized women were excluded from the study. Women who were seropositive for HIV infection and in whom pap smear results were available were taken as cases. Women who were seronegative for HIV infection and in whom pap smear results were available were considered as controls. Based on the inclusion and exclusion criteria, 60 women were identified as cases, and 270 women were identified as controls. For both cases and controls, from the case records, demographic details, such as age, socioeconomic status, parity, age at marriage, number of sexual partners, contraceptive use, examination findings of cervix, the details of pap smear abnormalities, and their further evaluation were noted. For HIV-positive women, further details such as CD4 count and the duration of antiretroviral therapy were also noted.

### Statistical Analysis

Mean and standard deviation were used for quantitative variables, frequency, and proportion for categorical variables. In order to check the normal distribution of quantitative variables, Shapiro-wilk test was used. For normally distributed quantitative parameters, the mean values were compared between cases and controls using independent sample *t*-test. Mann-Whitney *U* test was used for non-normally distributed quantitative parameters. Categorical outcomes were compared between the study groups using Chi-square test/Fisher's Exact test. *p*-value < 0.05 was considered statistically significant.

## RESULTS

This study included 330 subjects; 270 (81.82%) subjects were seronegative and 60 (18.18%) were seropositive for HIV infection. All women belonged to lower socioeconomic status. In both the cases and controls, conventional method had been used for pap smear testing. The mean age of control group was  $39.50 \pm 9.10$  and that of the cases was  $31.97 \pm 6.61$ , and the mean difference between two groups was statistically significant (*p*-value < 0.001). Among the controls, 191 (70.74%) women were above the age of 35 years, whereas in the cases group, 40 (66.7%) were younger than 35 years and majority (36.67%) of the subjects were aged between 25 and 29 years. The mean age at first coitus in the control group was  $19.21 \pm 2.74$  and it was  $20.52 \pm 4.30$  in the cases group, the mean difference between the groups was significant. The difference in the number of children between the seronegative women and seropositive women was also significant with a *p*-value < 0.001. In the control group, majority of the participants, that is, 128 (47.41%) had three or more children, whereas in the cases group, only 6 (10%) had three or more children (Table 1). On analyzing the contraceptive use, in

**Table 1:** The demographic characteristics of HIV-seronegative and seropositive women

| Parameter              | Study group       |                | <i>p</i> -value |
|------------------------|-------------------|----------------|-----------------|
|                        | Control (N = 270) | Cases (N = 60) |                 |
| Age                    |                   |                |                 |
| Mean                   | 39.50 ± 9.10      | 31.97 ± 6.61   | <0.001          |
| 20–24 Years            | 8 (2.96%)         | 4 (6.67%)      |                 |
| 25–29 Years            | 42 (15.56%)       | 22 (36.67%)    |                 |
| 30–34 Years            | 29 (10.74%)       | 14 (23.33%)    |                 |
| 35–39 Years            | 48 (17.78%)       | 11 (18.33%)    |                 |
| 40–44 Years            | 49 (18.15%)       | 4 (6.67%)      |                 |
| 45–49 Years            | 55 (20.37%)       | 5 (8.33%)      |                 |
| > = 50 Years           | 39 (14.44%)       | 0 (0.00%)      |                 |
| Age at first coitus    |                   |                |                 |
| Mean                   | 19.21 ± 2.74      | 20.52 ± 4.30   | 0.0033          |
| < = 14 Years           | 7 (2.59%)         | 3 (5.00%)      | 0.0037          |
| 15–19 Years            | 133 (49.26%)      | 22 (36.67%)    |                 |
| 20–24 Years            | 122 (45.19%)      | 27 (45.00%)    |                 |
| > = 25 Years           | 8 (2.96%)         | 8 (13.33%)     |                 |
| Parity                 |                   |                |                 |
| No children            | 9 (3.33%)         | 5 (8.33%)      | <0.001          |
| One                    | 20 (7.41%)        | 24 (40.00%)    |                 |
| Two                    | 113 (41.85%)      | 25 (41.67%)    |                 |
| Three or more children | 128 (47.41%)      | 6 (10.00%)     |                 |

**Table 2:** Contraceptive use by the participants

| Contraception      | Study group       |                |
|--------------------|-------------------|----------------|
|                    | Control (N = 270) | Cases (N = 60) |
| Tubectomy          | 195 (72.22%)      | 13 (21.67%)    |
| Condom             | 0 (0.00%)         | 17 (28.33%)    |
| IUCD               | 13 (4.81%)        | 0 (0.00%)      |
| Tubectomy + Condom | 0 (0.00%)         | 16 (26.67%)    |
| Nil                | 62 (22.96%)       | 14 (23.34%)    |

the control group 72.2% of women had undergone tubectomy and 4.81% had used intrauterine contraceptive device and none had used condom. Whereas, among the seropositive women, 48.4% had undergone tubectomy and condom use was seen in nearly 55% of the women (Table 2). There was no documented history of multiple partners in HIV-negative women, whereas, among the HIV-seropositive women, 95% of the male partners and 20% of female partners have had polygamous relationships.

On examination, unhealthy cervix was seen in nearly 36% of the seronegative women and in 41.5% of the seropositive women. On analyzing the pap smear abnormalities between the cases and controls, it was seen that in the control group, 5 (1.85%) women had pap smear abnormalities, whereas in the seropositive women 8 (13.33%) had pap smear abnormalities, and the difference between the groups was found to be significant with a *p*-value of < 0.001 (Table 3). On analyzing the pap smear abnormalities, among seropositive women, there were 3 cases of ASCUS (atypical squamous cells of undetermined significance), 3 cases of LSIL (low-grade squamous intra epithelial lesion), one case

**Table 3:** Pap smear abnormalities among the cases and controls (N = 330)

| Normal/<br>abnormal pap<br>smear               | Study group          |                   | Chi-square<br>value | p-value |
|--|----------------------|-------------------|---------------------|---------|
|  | Control<br>(N = 270) | Cases<br>(N = 60) |                     |         |
| Negative for<br>intraepithelial<br>lesion      | 265 (98.15%)         | 52 (86.67%)       | 17.10               | <0.001  |
| Positive for<br>squamous cell<br>abnormalities | 5 (1.85%)            | 8 (13.33%)        |                     |         |
| <i>Abnormalities noted on pap smear</i>        |                      |                   |                     |         |
| Pap report                                     | Control (N = 270)    |                   | Cases (N = 60)      |         |
| Atrophic<br>smear                              | 27 (10%)             |                   | 0 (0.00%)           |         |
| Inflammatory<br>smear                          | 128 (47.41%)         |                   | 37 (61.67%)         |         |
| ASCUS  | 3 (1.11%)            |                   | 3 (5.00%)           |         |
| LSIL   | 2 (0.74%)            |                   | 3 (5.00%)           |         |
| HSIL   | 0 (0.00%)            |                   | 1 (1.67%)           |         |
| SCC  | 0 (0.00%)            |                   | 1 (1.67%)           |         |
| Normal smear                                   | 110 (40.74%)         |                   | 15 (25.00%)         |         |

of HSIL (high-grade squamous intra epithelial lesion) and one case of invasive squamous cell carcinoma. Whereas among seronegative women, there were 3 reports of ASCUS and 2 cases of LSIL. Besides, the incidence of inflammatory smear was 61.7% among seropositive women and 47% among seronegative women (Table 3). In those diagnosed with abnormal smears, further evaluation was carried out and the colposcopy directed biopsy showed 3 cases of high-grade lesions, one case of infiltrating squamous cell carcinoma, 3 cases of low-grade lesions and one chronic cervicitis among HIV-positive women, whereas among the seronegative women, 3 cases were low-grade lesions and two were reported as chronic cervicitis.

Among the seropositive women, except two women, all the others have used antiretroviral therapy (ART) for a varying period of time. The mean duration of ART use was 3.89 years; nearly 50% of them have used antiretroviral therapy for 2–4 years and another 30% have used for more than 4 years. Statistically, the association between the duration of drug use and frequency of abnormal smears was insignificant (*p*-value 0.3590) (Table 4). Among 60 HIV-seropositive women, CD4 count was available in 58 women and the mean CD4 count was  $534.34 \pm 242.24$ . In 64.14% of cases, the CD4 count was >400. When pap smear abnormalities were correlated with CD4 count, it was seen that nearly 60% of abnormalities were seen even when the CD4 count was >400 (Table 4).

In order to see whether the abnormal pap smear results were influenced by the various risk factors, univariate logistic regression analysis was carried out and it showed that there was no statistically significant association between the abnormal pap smear results, age of the individual, age at first coitus and parity in both cases and controls (Table 5).

## DISCUSSION

It has been shown that 5% of cervical cancer cases are seen in women with HIV and these women are six times more likely to develop cervical cancer compared with women without HIV.<sup>15</sup> The risk of HIV-related mortality is also two-fold higher than

**Table 4:** Association between duration of antiretroviral therapy, CD4 count and pap smear abnormalities among HIV-positive women (N = 58)

| Duration of ART use | Normal smear<br>(N = 52) | Abnormal smear<br>(N = 6) |                     |
|---------------------|--------------------------|---------------------------|---------------------|
| <2 Years            | 10 (19.23%)              | 1 (16.67%)                | 0.3590 <sup>†</sup> |
| 2–4 Years           | 28 (53.85%)              | 1 (16.67%)                |                     |
| 4.01–6 Years        | 6 (11.54%)               | 2 (33.33%)                |                     |
| 6.01–8 Years        | 4 (7.69%)                | 1 (16.67%)                |                     |
| >8.01 Years         | 4 (7.69%)                | 1 (16.67%)                |                     |
| CD4 count           |                          |                           |                     |
| <200 (N = 3)        | 3 (100.00%)              | 0 (0.00%)                 |                     |
| 200–399 (N = 16)    | 14 (87.50%)              | 2 (12.50%)                |                     |
| 400–599 (N = 16)    | 15 (93.75%)              | 1 (6.25%)                 |                     |
| 600–799 (N = 13)    | 11 (84.62%)              | 2 (15.38%)                |                     |
| > = 800 (N = 10)    | 9 (90.00%)               | 1 (10.00%)                |                     |

those women who are HIV-negative.<sup>16</sup> Immunosuppression is an important cause for HPV infection to progress to cervical cancer. Most sexually active women are infected by HPV, but the infection is cleared by the immune system. However, in women with weak immune system, the risk of having persistent HPV infection is increased. Studies have shown that women infected with HIV are at increased risk of acquiring and persistence of high-risk human papilloma virus infection, increased risk of progression to pre-malignant and invasive cervical cancer as compared with HIV-negative women.<sup>11–13</sup>

In a study from India, pap smear abnormalities were noted in 30% of the HIV-positive women.<sup>17</sup> Gupta et al. reported that pap smear abnormalities were twice higher in HIV-infected women (12%) as compared with HIV-negative women (6%).<sup>18</sup> Our study also showed a higher prevalence of pap smear abnormalities at 13.3% among HIV-positive women compared with 1.85% among HIV-negative women which is statistically significant. On further evaluation of pap smear abnormalities, among the seropositive women, there was higher incidence of high-grade lesions with HSIL and SCC seen in 1.67% of cases each, whereas among the seronegative women, either low-grade lesion or chronic cervicitis was noted. The incidence of HSIL and SCC found in Gupta et al. study among seropositive women was 3.4% and 0.8%, respectively.<sup>18</sup> Massad et al. study also showed that CIN 3 and CIN 2 lesions were three times higher among seropositive women as compared with seronegative women.<sup>12</sup> Besides the pap smear abnormalities, a higher incidence of inflammatory smear was also noted in both the groups; 61.7% among seropositive women and 47% among seronegative women. Similar to our study, a high incidence of inflammatory smears was also noted in the study of Seethalakshmi et al. About 51.96% among HIV-positive women and 43.75% among HIV-negative women.<sup>19</sup> The above findings highlight the need for re-evaluation by follow-up pap smears/Colposcopy to exclude pre-invasive and invasive cervical lesions especially in seropositive women.

In women with normal immune system, it may take 20 years for cervical cancer to develop. However, in women with weak immune system such as those with untreated HIV infection, cervical cancer may develop within 10 years. Compromised immune status plays an important role in acquiring the HPV infection and its persistence.<sup>20</sup> Studies have shown that the risk of developing

**Table 5:** The association between the risk factors (age of the individuals, age at first coitus and parity) and abnormal pap smear results among the controls and cases (N = 330)

|                            | Controls                |        |                         |        | Cases                  |        |                         |        |
|----------------------------|-------------------------|--------|-------------------------|--------|------------------------|--------|-------------------------|--------|
|                            | Normal smears (N = 265) |        | Abnormal smears (N = 5) |        | Normal smears (N = 52) |        | Abnormal smears (N = 8) |        |
|                            | No.                     | %      | No.                     | %      | No.                    | %      | No.                     | %      |
| <b>Age group</b>           |                         |        |                         |        |                        |        |                         |        |
| 20–24 Years                | 8                       | 3.02%  | 0                       | 0.00%  | 4                      | 7.69%  | 0                       | 0.00%  |
| 25–29 Years                | 42                      | 15.85% | 0                       | 0.00%  | 21                     | 40.38% | 1                       | 12.50% |
| 30–34 Years                | 29                      | 10.94% | 0                       | 0.00%  | 12                     | 23.08% | 2                       | 25.00% |
| 35–39 Years                | 47                      | 17.74% | 1                       | 20.00% | 8                      | 15.38% | 3                       | 37.50% |
| 40–44 Years                | 47                      | 17.74% | 2                       | 40.00% | 2                      | 3.85%  | 2                       | 25.00% |
| 45–49 Years                | 54                      | 20.38% | 1                       | 20.00% | 5                      | 9.62%  | 0                       | 0.00%  |
| > = 50 Years               | 38                      | 14.34% | 1                       | 20.00% | 0                      | 0.00%  | 0                       | 0.00%  |
| <b>Age at first coitus</b> |                         |        |                         |        |                        |        |                         |        |
| < = 14 Years               | 7                       | 2.64%  | 0                       | 0.00%  | 2                      | 3.85%  | 1                       | 12.50% |
| 15–19 Years                | 129                     | 48.68% | 4                       | 80.00% | 19                     | 36.54% | 3                       | 37.50% |
| 20–24 Years                | 122                     | 46.04% | 0                       | 0.00%  | 23                     | 44.23% | 4                       | 50.00% |
| > = 25 Years               | 7                       | 2.64%  | 1                       | 20.00% | 8                      | 15.38% | 0                       | 0.00%  |
| <b>Parity</b>              |                         |        |                         |        |                        |        |                         |        |
| Zero                       | 9                       | 3.40%  | 0                       | 0.00%  | 4                      | 7.69%  | 1                       | 12.50% |
| One                        | 20                      | 7.55%  | 0                       | 0.00%  | 22                     | 42.31% | 2                       | 25.00% |
| Two                        | 112                     | 42.26% | 1                       | 20.00% | 20                     | 38.46% | 5                       | 62.50% |
| Three or more children     | 124                     | 46.79% | 4                       | 80.00% | 6                      | 11.54% | 0                       | 0.00%  |

pre-invasive and invasive cervical lesions is inversely proportional to CD4+ T-lymphocyte counts.<sup>21</sup> Study by Prathima et al. has shown that CD4 count <350 cells/microliter was a significant risk factor associated with abnormal pap smear.<sup>22</sup> However, in our study, in 64.14% of cases, the CD4 count was >400 and when pap smear abnormalities were correlated with CD4 count, it was seen that nearly 60% of abnormalities were seen even when the CD4 count was >400. Similar to our study, the studies of Madan et al. and Gupta et al. also did not show significant association between pap smear abnormalities and CD4 cell count.<sup>17,18</sup>

It has been shown that ART can improve the health of HIV patients by improving their immunological status, preventing opportunistic infections like HPV, thereby preventing cervical epithelial abnormalities. Though the incidence of cervical epithelial abnormalities has reduced after the introduction of the highly active antiretroviral therapy (HAART), the risk of progression to high-grade intraepithelial lesions and cervical cancer is still high among HIV-infected women.<sup>23</sup> In our study, the association between the duration of antiretroviral therapy and frequency of abnormal smears was insignificant. It has been shown that HIV-infected women develop cervical cancer at a younger age. In our study, among seropositive women, pap smear abnormalities were predominantly seen in younger women; 75% were <39 years of age and 36.67% were between 25 and 29 years of age. Whereas among seronegative women, all women with pap smear abnormalities were more than 39 years of age. As in our study, Madan et al. also showed that among the HIV-positive women, the highest incidence of intraepithelial lesions was seen in women of 31–40 years of age.<sup>17</sup> Whereas, in Gupta et al. study, women in the age group of 34–49 years showed the highest incidence of intraepithelial lesions in HIV-positive women.<sup>18</sup>

In our study, on univariate logistic regression analysis, there was no significant association between the cytological abnormalities,

the age of the individual, age at first intercourse, and parity in both cases and controls. These findings show that in HIV-positive women, the immunosuppression is the predominant risk factors leading to pap smear abnormalities. Similar to our findings, the study of Gaym et al. also did not show a significant association between cytological abnormalities and age at first sexual contact, and parity.<sup>24</sup> However, Prathima et al. have shown in their study a significant association between age at first sexual intercourse, history of sexually transmitted infections, husbands having multiple sexual partners and pap smear abnormalities among HIV-positive women.<sup>22</sup>

## CONCLUSION

Globally, as well as in India, cervical cancer prevention is an important health priority. In our study, pap smear abnormalities were seven times more among HIV-infected women compared with HIV-negative women. Despite being on effective ART, seropositive women still show a high prevalence of pap smear abnormalities. The frequency of inflammatory smears is also more among these women. Clinical significance of this study is that besides effectively integrating cervical cancer screening programs with HIV treatment services, there should be more frequent gynecologic and pap smear evaluation in these women to detect preinvasive lesions so that invasive cervical cancer can be prevented. It is also important that in women presenting with inflammatory smears, underlying preinvasive lesions should not be missed, therefore, they should be evaluated further.

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