ABSTRACT: BACKGROUND: Cancer cervix is the second most common cancer in women. Infection with HPV has been implicated in pre-cancerous squamous intraepithelial lesions and their progression to cervical cancer. The risk of infection with HPV is augmented in the presence of HIV infection. Hence we conducted this study to assess the difference in occurrence of cervical intraepithelial lesions in HIV positive and HIV-negative patients. METHODS: 100 women attending the ART centre and gynaec OPD were chosen, out of which, about half were HIV positive and the other half were HIV negative. Each of them underwent Pap smear examination signing a written consent. The smears were sent to pathologists for evaluation. After cytological examination, the cervical squamous intraepithelial lesions were classified based on their cytomorphological features. RESULTS: In the HIV-negative category, the prevalence of squamous cell abnormality in the age group 31-40 was 14.3% and in the age group 41-50 was 20%. In the HIV positive category, increased incidence of squamous cell abnormality was found in the age group 31-40 (26.7%). This indicates that squamous cell abnormality in the HIV positive category had high prevalence in the younger age group. CONCLUSION: In conclusion, HIV infection appears to alter the spectrum of HPV infection and its further development into pre-cancerous lesion and invasive cancer. We also noted that the intraepithelial lesions tend to occur at an early age in HIV positive women. This may be attributed to any alterations in the local response of the genital tract induced by HIV or due to the paucity of cell mediated immunity. Hence high priority must be given for early screening process to detect the cervical lesions at the earliest among HIV positive women in order to prevent them from developing into invasive cancer.

KEYWORDS: Cervical lesion, HIV, Pap smear.

INTRODUCTION: Approximately 274000 of the half of a million women who develop cervical cancer annually will die from the disease.1 Cervical cancer is the second most common cancer in women globally and accounts for 13% of all female cancers.

Cervical cancer is mostly (99%) linked to genital infection with human papillomavirus (HPV), of which there are over 100 types. High risk human papillomavirus especially HPV types 16 and 18 is estimated to cause all cervical cancer cases.2 Persistent infection by oncogenic HPV types is a pre-requisite for the development of cervical cancer. Normal cells of the cervix usually first develop pre-cancerous changes which may progress to cancer. The pre-cancerous changes are graded as cervical intraepithelial neoplasia (CIN), squamous intraepithelial lesion (SIL) and dysplasia.
HIV is a global pandemic. As of 2011, approximately 34 million people have HIV worldwide. Of these approximately 16.8 million are women.

HIV infected individuals are at higher risk of HPV infection and persistence and are infected by a broader range of HPV types. Both HIV and HPV are sexually transmitted and infection with either is known to facilitate infection with the other.

Women living with HIV have been found to be 8 times more likely to develop invasive cervical cancers than women who were not HIV infected.\[^3\]

HIV may increase the risk of progression of cervical cancer.\[^4\] Immune deficiency increases the risk of cervical disease progression because HIV appears to alter the natural history of HPV infection, causing a much more rapid progression to high grade and invasive lesion which are refractory to treatment.

Pre-cancerous cells in the cervix can be detected early by a Papaniclaou test, commonly known as Pap smear.\[^5\]

As women with HIV are at higher risk, screening of cervical epithelial changes and appropriate intervention in women with intraepithelial lesions are effective in preventing cervical cancer in the HIV-positive category.

Screening HIV-infected patients for squamous cell cancer of the cervix and human papillomavirus-related cervical dysplasia may prevent excess morbidity and mortality.

Raichur, a remote district in the north-eastern part of Karnataka witnesses a high incidence of HIV due to lack of literacy and education. The present research was conducted in RIMS teaching hospital to establish the increased risk of developing cervical cancer in the HIV women as compared to the HIV non infected women. The study was conducted for a period of two months i. e. May 2013 to June 2013.

**REVIEW OF LITERATURE:** An extensive literature survey of existing research work pertaining to the subject was conducted and it was found that works were carried to establish the relation between HIV and cervical intraepithelial changes.

In 2003 Schuman P. et al examined and correlates of progression and regression of abnormal cervical cytologic test results in 774 HIV seropositive and 391 HIV sero negative and monitored them semi-annually for upto 5.5 years. The results obtained support the present finding.

In 2001, S. Joshi et al carried out a study to assess the frequency of Pap smear abnormalities and its association with HIV infection women attending STD clinics and also to identify associated risk factors. The results were supporting the present study that HIV is one of the co-factors for the persistence of HPV infection and invasive cervical cancer.

A number of other related work were carried out by many researchers, most of which established the relation between HIV infection and cervical intraepithelial changes and also suggested regular screening and follow-up in these women.

**AIMS AND OBJECTIVES:** This is a prospective study that aims at establishing the increased incidence of cervical intraepithelial changes in women with HIV as compared to the non-HIV infected using the routine pap smear.
This study can help in the early detection of the cervical intraepithelial changes in the HIV infected category. The early detection could be followed by appropriate intervention at early stages to save many lives.

MATERIALS AND METHODS: This study was done to establish the difference of occurrence of cervical intraepithelial changes in women infected with HIV and those not infected with HIV.

Type: Prospective study.

Duration of Study: 2 Months.

Study Site and Population: This study was carried out in about 100 patients attending the ART centre and OBG OPD in Raichur Institute of Medical Sciences, Raichur. Out of these, half were known HIV infected women and the other half were HIV negative.

The subjects underwent a general physical examination and answered questions pertaining to the medical and sexual history. They underwent a detailed interview regarding their sexual behaviour that includes questions about marital history, age at menarche, age at first intercourse, number of sexual partners.

Selection Criteria: 50 HIV infected and 50 HIV- non infected women were included in this study.

An informed consent was obtained from the patients.

The samples were not taken during menstrual bleeding.

METHODS: The method used in this study was cytological using the Pap smears.[6]

MATERIALS:
- Cusco’s speculum.
- Retractor.
- Medscand disposable cytobrush.
- Ayres spatula.
- Biofix.
- Glass slides.
- Papanicolaou stain.

SAMPLE COLLECTION:
- The sample was obtained under direct vision.
- The women were asked to lie down in lithotomy position and Cusco’s speculum was inserted into their vagina and the retractor was used to retract the anterior vaginal wall to get a clear view of the cervix.
- Using the Ayre’s spatula and cytobrush, a total of 3 samples were taken one each from the endocervix, the transition zone and the posterior fornix of vagina.
- The materials were then smeared onto the glass slide.
- Biofix was sprayed on the smears.
- It was then transported to the pathology lab.
STAINING: Papanicolaou stains were used to stain the wet fixed smear.

EVALUATION:
- It was then evaluated by 2 cytopathologist blinded to the HIV status of the patients.
- Two cytopathologists carried out the evaluation so as to avoid any observer variations.
- Slides with scanty epithelial components, inadequately fixed slides, and those slides with obscuring blood or artefacts were rejected.
- After screening, the cervical squamous intraepithelial lesions were classified based on their cytomorphological features. For analysis, Pap test reports were categorized as normal, inflammatory, ASCUS, lowgrade squamous intraepithelial lesions (SIL) and high grade SIL. Women with ASCUS, LSIL, HSIL were categorised as having squamous cell abnormality.

OBSERVATIONS AND RESULTS: 100 women were chosen out of which 50 were known HIV positive and the remaining 50 were HIV negative.
- The results obtained from the two pathologists did not vary significantly.
- Mean age of marriage: 20 years.

HIV NEGATIVE CASES: The total number of cases in the HIV negative category=50.
- For the non-HIV category the age distribution is as follows.

| Age   | Number of women | Percentage |
|-------|-----------------|------------|
| 21-30 | 28              | 56%        |
| 31-40 | 7               | 14%        |
| 41-50 | 6               | 12%        |
| 51-60 | 9               | 18%        |

Table 1: Age Distribution

![Figure 1](image-url)
HIV POSITIVE CASES:

| AGE   | NUMBER OF WOMEN | PERCENTAGE |
|-------|-----------------|------------|
| 21-30 | 8               | 16%        |
| 31-40 | 15              | 30%        |
| 41-50 | 25              | 50%        |
| 51-60 | 2               | 4%         |

Table 2: Observation and Results of Pap Smear

HIV NEGATIVE:

TOTAL NUMBER: 50.
Out of these 6 were unsatisfactory and not suitable for evaluation.
So the total is 44.

| Pap Smear result               | Number of women | Percentage |
|--------------------------------|-----------------|------------|
| Within normal limits           | 32              | 72.7%      |
| Inflammatory smears            | 10              | 22.7%      |
| Squamous cell abnormality      | 2               | 4.6%       |

Table 3
The table and chart indicates that in the HIV-negative group, 32 women out of 44 (72.7%) had the cervical smears within the normal limits. Out 44, 10 women (22.7%) had inflammatory smears. And only 2 of them out of 44 (4.6%) showed squamous cell abnormality. The Squamous cell abnormality in both these cases was atypical Squamous cells of undetermined significance.

**HIV POSITIVE:**

Total number of cases = 50.
Out of these 4 were unsatisfactory and not suitable for evaluation.
Therefore, total = 46.

| Pap smear result          | Number of women | Percentage |
|---------------------------|-----------------|------------|
| Within normal limits      | 21              | 45.7%      |
| Inflammatory smears       | 18              | 39.1%      |
| Squamous cell abnormality | 7               | 15.2%      |

Table 4

Table and chart indicates that in the HIV positive group, 21 out of 46 (45.7%) showed normal pap smears. 18 women out of 46 (39.1%) showed inflammatory smears and also, there were 7 women (15.2%) who had squamous cell abnormalities. Among these, 5 were categorised as having atypical cells of undetermined significance and 2 was found to be LSIL.

**AGE DISTRIBUTION WITH PAP SMEAR RESULTS:**

**TABLE 3: HIV NEGATIVE:**

| Pap smear result          | Number of women | Percentage |
|---------------------------|-----------------|------------|
| within normal limits      | 24              | 88.9%      |
| inflammatory             | 3               | 11.1%      |
| Squamous-cell abnormality | nil             |            |

Table 3a: Age group 21-30
Pap Smear Result | Number of Women | Percentage
---|---|---
Within normal limits | 2 | 28.6%
Inflammatory | 4 | 57.1%
Squamous-cell abnormality | 1 | 14.3%

Table 3b: Age group 31-40

Pap Smear Result | Number of Women | Percentage
---|---|---
Within normal limits | 2 | 40%
Inflammatory | 2 | 40%
Squamous-cell abnormality | 1 | 20%

Table 3c: Age group 41-50
**Pap Smear Result** | **Number of Women** | **Percentage**
--- | --- | ---
Within normal limits | 4 | 80%
Inflammatory | 1 | 20%
Squamous-cell abnormality | Nil | 

Table 3d: Age group 51-60

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**Pap Smear Result** | **Number of Women** | **Percentage**
--- | --- | ---
Within normal limits | 3 | 42.9%
Inflammatory | 3 | 42.9%
Squamous-cell abnormality | 1 | 14.2%

Table 4a: Age group 21-30

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**Pap smear result** | **Number of Women** | **Percentage**
--- | --- | ---
Within normal limits | 7 | 46.6%
Inflammatory | 4 | 26.7%
Squamous-cell abnormality | 4 | 26.7%

Table 4b: Age group 31-40
### Table 4c: Age group 41-50

| Pap Smear Result                | Number of Women | Percentage |
|---------------------------------|-----------------|------------|
| Within normal limits            | 11              | 47.8%      |
| Inflammatory                    | 10              | 43.5%      |
| Squamous-cell abnormality       | 2               | 8.7%       |

### Table 4d: Age group 51-60

| Pap smear result                | Number of Women | Percentage |
|---------------------------------|-----------------|------------|
| Within normal limits            | Nil             | 100%       |
| Inflammatory                    | 1               | 100%       |
| Squamous-cell abnormality       | Nil             |            |
The above data depicts that the pap smear abnormalities are more prevalent in younger age group in the HIV-positive category than in the HIV negative category.

**DISCUSSION:** As there is an increase in the epidemic of HIV in the general population, and more importantly women, an increased risk of cervical intraepithelial lesions and cervical cancer can be anticipated.

This study was done with the help of Pap smear. Pre-cancerous cells in the cervix can be detected by Pap smear.

In the present study, HIV seropositive women had higher prevalence of squamous cell abnormality in Pap smear compared to those who were seronegative. (Table 2)

HIV positive women were at approximately three times likely to have squamous cell abnormality and abnormal Pap smear than HIV negative women.

The association between HIV and squamous cell abnormality was varied in different age groups.

In the HIV-negative category, the prevalence of squamous cell abnormality in the age group 31-40 was 14.3% and in the age group 41-50 was 20% (table 3b and 3c). In the HIV positive category, increased incidence of squamous cell abnormality was found in the age group 31-40(26.7%) (Table 4b). This indicates that squamous cell abnormality in the HIV positive category had high prevalence in the young age group. This result is similar to that obtained in Nigeria where majority of the women were aged between 30 and 39 and the median age observed for an invasive cancer diagnosis or positive screening result was 32 years, which is less than 10 years younger than the median age of 47 years for cervical cancer diagnosis in general population.

A possible explanation to this observation is the HIV-induced immune suppression which can contribute to the development of squamous cell abnormalities and further to cervical cancer.[7] Alterations of the local immune response of the genital tract caused by the HIV infection may be the reason for higher prevalence and progression rates of cervical intraepithelial lesions in these women.

HIV associated, cell-mediated immunocompromise may increase risk for HPV infection, promote reactivation of latent infection, or permit HPV persistence, resulting in increased risk of cervical dysplasia.

HIV appears to alter the natural history of HPV infection, causing a much more rapid progression to high-grade and invasive lesions that are refractory to treatment or which are slow to regress.

Some researchers suggest this more aggressive course may actually be due to an HIV-related change in the molecular pathway leading to cervical cancer, possible due to an interaction between viral proteins, with HIV proteins enhancing the effectiveness of HPV proteins and perhaps contributing to cell cycle disruption[8]

A 2006 pilot study to assess the need for cervical screening among women with HIV in Zambia showed that among a cohort of 150 women, almost one in five had signs suggestive of cervical cad a normal pap smear. Almost 50% had high-grade cervical cancer changes.[9] Cervical cytology appears to be adequate as a screening tool for detection of CIN in HIV seropositive
women and many studies have stressed a need for careful interpretation, further evaluation with colposcopy and directed biopsy and follow up.

These results highlight the importance of increasing the capacity of cervical cancer screening programs and the availability of treatment. Cervical cancer is preventable by screening of pre-cancerous lesions and appropriate therapy.

High priority should be given to the development of innovative and cost–effective methods of screening for and treating squamous intraepithelial lesions in HIV infected.

**CONCLUSION:** These data support the hypothesis that HIV infection is a cofactor for cervical cancer in women with HPV infection, and, as in all populations, the need for promoting cervical screening in populations with high prevalence of HIV infection.

In this study population who had a Pap smear, cervical cancer was observed at a younger age among women with HIV infection.

On the basis of this study, it can be concluded that there is an increased incidence of cervical intraepithelial changes in HIV positive category as compared to the HIV negative category.

The findings overall add support to the association of squamous cell abnormality among HIV infected women, an association on which the recommendation for annual cervical cytology screening in persons with HIV infection is based.

**SUMMARY:**

**PURPOSE OF THE STUDY:**

Hypothesis: there is an increased risk of cervical intraepithelial changes in the HIV positive women as compared to the HIV negative category.

Objective: To establish the increased incidence of cervical intraepithelial changes in HIV infected women as compared to the HIV negative women using Pap test.

**DESCRIPTION:** Cervical abnormalities can be detected using Pap smears.

50 HIV positive and 50 HIV negative women were chosen for the study and they underwent the Pap test.

**RESULTS:** Among the satisfactory smears in the HIV positive category, squamous cell abnormality was found in 15.2% of the women and only 4.6% had squamous cell abnormality in the HIV non infected category.

**CONCLUSION:** The data presented here confirmed the higher incidence of cervical intraepithelial lesions in HIV positive women than in HIV negative women. Hence screening and appropriate intervention at the right time can help halt the development of cervical cancer in the HIV infected category.
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