

A Study of Pap Smear in HIV-Positive Females

Apeksha Madan¹ · Sunita Patil² · Leena Nakate³

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About the Author



Dr. Apeksha Madan was a secondary D.N.B pathology resident at R.C.S.M Government Medical College, Kolhapur, from February 2013 to February 2015. She has given her practical exams and is awaiting results. She is currently working as a Pathologist at SRL Diagnostics, Mumbai. Pap smear was her thesis topic. This being a tertiary care hospital, prevalence of abnormalities in Pap smear in HIV females on antiretroviral therapy is high. Pap smear interpretation is her field of interest.

Abstract

Background HIV-positive females are more likely to have abnormal Pap smears than HIV-negative women. These abnormal Pap smears are usually associated with low CD4 cell counts and human papilloma virus infection. **Materials and Methods** This was a prospective hospital-based study from April 2013 till March 2014. A total of 250 (both symptomatic and asymptomatic) HIV-positive

females were examined in Gynaecology OPD at R.C.S.M. G.M.C and C.P.R. Hospital, Kolhapur, and their cervical smears were taken. They were categorized as per modified Bethesda system 2001. The findings in HIV-positive women were correlated with risk factors (age, disease duration, CD4 count and ART use).

Aims To study the spectrum of cytological abnormalities on Pap smear in HIV-positive females and classify pre-cancerous and cancerous lesions in HIV-positive females according to Bethesda system 2001 and to be familiar with terminology and morphological criteria of Bethesda system 2001. To study the association of Pap smears abnormalities among HIV-positive women with their immune status (CD4 count).

Results NILM is the commonest finding (83.2 %) which is subdivided into non-inflammatory, non-specific and specific inflammatory and atrophic smears. Candida vaginitis was the commonest cause of specific inflammatory condition accounted for (2.52 %) of all inflammatory

Dr. Apeksha Madan, D.P.B. Pathologist at SRL Diagnostics;
Dr. Sunita Patil, Associate Professor at Dr B R Ambedkar Medical College; Dr. Leena Nakate, Professor at B J Medical College.

✉ Apeksha Madan
drapeksha2009@gmail.com

¹ SRL Diagnostics, Mumbai, India

² Dr. B R Ambedkar Medical College, Bangalore, India

³ B J Medical College, Pune, India

smears. The percentage of squamous cell abnormalities was 12 %: ASCUS + ASC-H—6.22 %, LSIL—2.10 %, HSIL—3.4 % and SCC—0.8 %. The highest incidence of intraepithelial lesions in HIV-positive females was in the age group 31–40 years. There is no association of Pap smear abnormalities among HIV-positive women with their immune status (CD4 count) and duration of ART.

Conclusion Periodic, regular gynaecologic and Pap smear examination would help in early detection of intraepithelial lesions and their treatment so as to prevent invasive malignancy and mortality.

Keywords HIV · Squamous cell abnormalities · Intraepithelial lesions · Pap smear

Abbreviations

&	And
AGC	Atypical glandular cell
ART	Antiretroviral therapy
ASC-H	Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion
ASCUS	Atypical squamous cells of undetermined significance
BV	Bacterial vaginosis
CA	Candida
CDC	Centres for Disease Control and Prevention
CD4	Cluster of cell differentiation
CIN	Cervical intraepithelial lesion
CIS	Carcinoma in situ
Cx	Cervix
EA	Eosin azure
EC/TZ	Endocervical/transformation zone
FGT	Female genital tract
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
HSV	Herpes simplex virus
HSIL	High-grade squamous intraepithelial lesion
i.e.	That is
IUCD	Intrauterine contraception device
K/C/O	Known case of
LBC	Liquid-based cytology
LEEP	Loop electrosurgical excision procedure
LGTI	Lower genital tract infections
LMP	Last menstrual period
LSIL	Low-grade squamous intraepithelial lesion
N:C ratio	Nuclear-to-cytoplasmic ratio
OG-6	Orange G-6
Pap	Papanicolau
P/S	Per speculum

Introduction

HIV-infected women have a higher risk of human papilloma virus (HPV)-associated cervical intraepithelial neoplasia as compared to HIV-uninfected women [1–5]. The overwhelming majority of women affected by this completely preventable disease reside in resource-constrained nations where access to screening services is limited or non-existent. In the same settings, during the past decade, the HIV/AIDS pandemic has overwhelmed the healthcare systems and had an enormous impact on women, particularly those of reproductive age [6–8].

HIV-seropositive females have a higher prevalence of HPV infection (due to immune compromised status) and are more likely to develop persistent HPV infection with multiple HPV genotypes thus are at greater risk (ten times increased risk) of developing cervical intraepithelial neoplasms and invasive cervical cancers [9, 10].

Pap smear examination is a simple, cheap, safe diagnostic tool for early detection of cervical cancer, that is to detect the presence of abnormal, atypical cells [9]. Pap smear also initiates the immunological clearance of HPV, thereby it helps to decrease morbidity and mortality due to cervical cancer in HIV-positive females [9].

However, increasing numbers of women are being linked to antiretroviral therapy treatment programs which have the potential to improve their lifespan long enough for cervical cancer precursors to manifest and progress to invasive cancer [6]. This study was carried mainly to detect precancerous and cancerous lesions as well as inflammatory lesions and to highlight the importance of a detailed gynaecological examination and cervical cytology in HIV-positive females, registered and attending antiretroviral treatment (ART) clinic, at R. C. S. M.G. M.C. and C. P. R. Hospital, Kolhapur.

Materials and Methods

This was a prospective study of 250 cases of HIV-positive females on/not on antiretroviral therapy attending Integrated Counseling and Testing Centre (ICTC), and the period of this study was from April 2013 to March 2014. A written informed consent was obtained from each study participant after providing details of the study through patient information sheet. After ethical committee clearance from the institute, this study is undertaken in collaboration with the Gynaecology department and ART centre, in the department of Pathology R.C.S.M.G.M.C. and

C.P.R. Hospital, Kolhapur. A detailed workup of the patient including age, marital status, occupation, duration, CD4 count, ART record (whether taking or not taking art) was recorded. Detailed clinical history obstetric and menstrual history along with clinical examination findings, per abdominal examination, per speculum examination, per vaginal examination and relevant findings were recorded. All females who were 18 years and above who were HIV positive were included. All patients who had undergone total hysterectomy were excluded. CD4 count was checked once in 6 months. All patients who had CD4 count <500 cells/mm³ were started ART.

Results

This study was conducted for a period of 1 year during this period we collected 250 Pap smears from HIV-seropositive females attending ICTC at C. P. R. Hospital and R. C. S. M. G. M. C., Kolhapur (Table 1).

A total of 12 smears (4.8 %) were considered unsatisfactory in the study due to non follow up visits by patients, thus excluded from the study. The commonest pattern observed was NILM which comprised of 208 cases (87.39 %). In the NILM category non-inflammatory smears were commonest 157 cases (66 %) followed by non-specific inflammatory 34 cases (14.28 %). These also included reactive cellular change associated with inflammation, repair and atrophy. Among the specific cases of inflammatory lesions, 6 (2.52 %) cases were of Candida followed by 5 (2.1 %) cases of Bacterial vaginosis and 4

(1.68 %) cases of *Trichomonas vaginalis*. However, no cases of tuberculosis, Herpes, Chlamydia were detected in the study.

Out of 6 cases of Candida vaginitis, 4 were taking ART for more than 6 months, and out of 5 cases of bacterial vaginosis, 4 were on ART for more than 6 months, and 2 cases of *Trichomonas* were on ART for more than 6 months. Two cases of trichomonas on ART greater than 6 months. Epithelial cell abnormalities were present in 30 smears (12.6 %), commonest being atypical squamous cell of undetermined significance (ASCUS) with 11 cases (4.62 %). ASC-H was seen in 4 cases (13.34 %). Five (2.10 %) cases of LSIL were observed. HSIL were observed in 8 cases (26.66 %), and 2 cases (6.66 %) of SCC were noted. No glandular cell abnormalities were found. Twenty smears (8 %) were unsatisfactory on account of scanty cellularity and/or obscured by inflammation.

Repeat smears 8 out of 20 were included which were 6 smears of NILM, 1 smear of ASCUS, 1 smear of LSIL.

Few of the smears showed koilocytic change in superficial epithelial cells suggesting HPV infection. No confirmatory tests for HPV done.

Patients whose Pap smears were categorized as ASCUS were advised repeat follow-up after 6 months. Only three patients came for repeat smear, and two had reverted back to normal and 1 was diagnosed as HSIL.

Eight cases (3.4 %) were categorized as high-grade squamous intraepithelial lesion (HSIL). These patients were advised follow-up after 3 months and colposcopic biopsy. Out of the eight patients, only one patient came for follow-up. She was further evaluated with colposcopic biopsy which had acetowhite areas and histopathological finding of CIS, CIN-2.

Most epithelial cell abnormalities ($n = 17$) were in the reproductive age group of 31–40 years out of which of ASCUS was commonest with six cases, three cases of ASC-H, 3 cases of LSIL, 3 cases of HSIL and 2 cases of SCC seen. Four cases in the age group of 21–30 years were observed with 3 cases of ASCUS and 1 case of HSIL. Four cases in the age group 41–50 years had 1 case of ASCUS, 1 case of ASC-H, 1 case of LSIL and 1 case of HSIL.

Due to effective family planning, most of the cases were seen in P2. Despite being aware of the seropositive status, majority of 180 cases (75.63 %) were not in the habit of using barrier contraception. Out of the 30 cases with epithelial abnormalities, 22 Pap smears were from patients who did not use any barrier contraception in which increased incidence of ASCUS ($n = 8$) and HSIL ($n = 7$) was found.

A total of 194 cases (81.51 %) did not have any P/V findings. 38 cases (15.96 %) had complains of P/V discharge in which, 29 had white watery discharge, 4 had curdy white, 3 had foul smelling, and 2 had mixed discharge. Six other cases (2.52 %) in which 2 cases of

Table 1 Distribution of cytologic smear results as per Bethesda system 2001

Number	Pap smear interpretation as per Bethesda	Number of cases	Percentage
1.	NILM	208	83.2
2.	Epithelial abnormalities	30	12
3.	Unsatisfactory	12	4.8
	Total	250	100
Thus			
1.	NILM	157	66
a.	Non-specific	34	14.28
b.	Candida	6	2.52
	B. vaginosis	5	2.1
	<i>T. vaginalis</i>	4	1.68
c.	Atrophy	2	0.8
2.	ASCUS + ASC-H	15	6.22
	LSIL	5	2.10
	HSIL	8	3.4
	SCC	2	0.8
	Total	238	100

Table 2 Association of ART treatment with Pap smear

Bethesda classification	ART treatment		Total
	No	Yes	
1 = NILM	13	195	208
2 = ASCUS	0	11	11
3 = ASC-H	0	4	4
4 = LSIL	0	5	5
5 = HSIL	1	7	8
6 = SCC	0	2	2
Total	14	224	238

Test	Chi-square tests		
	Value	<i>df.</i>	<i>p</i> value
Pearson's Chi-square test	1.607	5	0.9
Likelihood ratio	2.731	5	0.741

cystocele, 1 case of cervical erosion, 1 case of procidentia and 1 case of hypertrophied cervix were observed.

Majority of cases 116 (48.7 %) had CD4 count between 200–500 cells/cum². It was followed by 109 patients (45.8 %) with CD4 count of >500 cells/mm³ in which 12 cases had epithelial abnormalities. 13 cases (5.5 %) had CD4 count <200 with 3 cases of epithelial abnormalities. Thus, it was seen that females with CD4 count <500 were more at risk of developing epithelial abnormalities due to decreased immune status (Table 2).

ART treatment does not affect the development of epithelial abnormalities. Table 2 shows association between Pap findings and ART treatment. There was no significant association between Pap findings and CD4 count as *p* value >0.05.

There was borderline significant association between Pap findings and CD4 count as *p* value ≥ 0.05 and needs to be tested by extensive multivariate analysis.

Discussion

Human immunodeficiency virus (HIV)-infected women constitute one of the highest risk population subgroups for increased incidence and rapid progression of HPV-induced cervical intraepithelial neoplasia (CIN) and invasive cervical cancer [11]. Studies show HIV-infected women have high prevalence of HPV infection with multiple HPV type, thus having greater risk of epithelial abnormality [12]. The effectiveness of Pap smear in detecting CIN in HIV-infected women has been reported to have a sensitivity varying from 60 to 80 % where as specificity ranges from 65 to 85 % [10, 13].

Globally 15 % of all cancers in women are cervical cancer, while in Southeast Asia cancer of uterine cervix accounts for 20–30 % [14] of all cancers in women. The incidence of cancer cervix is low in the developed countries, i.e. only 20 %, because of effectiveness of screening programs conducted, proper follow-up and timely treatment. The present study was carried out to determine the incidence of intraepithelial abnormalities in HIV-positive females, attending ART centre, in C.P.R. hospital.

With HIV/AIDS becoming a modern global pandemic, and its association with cervical cancer and its precursor lesions, the present prospective study of estimating the cytological abnormalities in Pap smear in HIV-seropositive women, by cervical cytology in our hospital gains significance [15]. The incidence of cervical epithelial cell abnormalities is 12.60 % (Table 3).

Table 3 Distribution of cases as per Bethesda in various studies

No.	Parameters	Bagga et al. [16] (n = 136)	Gaym et al. [17] (n = 466)	Moodley et al. [18] (n = 109)	Liebenson et al. [19] (n = 84)	Chalermchokcharoenkit et al. [20] (n = 821)	Devi and Priya [15] (n = 252)	Jha et al. [9] (n = 407)	Present study (n = 238)
1.	No epithelial abnormality (in %)	65.4	83.4	34.5	79.76	84.6	92.86	87.8	87.39
2.	Epithelial abnormalities (in %)	34.6	16.9	66.5	20.24	15.4	7.14	8.34	12.60
	ASCUS	1.5	10.52	15.3	0	2.8	0.8	3.19	4.62
	ASC-H	–	–	1	0	0.6	–	0.73	1.68
	LSIL	5.9	5.15	40	19.05	8.5	4.37	2.7	2.10
	HSIL	2.2	4.36	10.2	1.19	3.5	1.2	1.47	3.36
	SCC	0.7	–	–	–	0.1	–	–	0.8
	AGUS	–	–	0	0	0	0.8	0.25	0

Table 4 Association of RTIs in HIV-positive females

Specific infection	Sharma [21] (n = 83)	Chalermchokcharoenkit et al. [20] (n = 821)	Goel et al. [22] (n = 40; %)	Jha et al. [9] (n = 407)	Present study (n = 238)
Candida vaginitis	34 %	19.4 %	18	1.78 %	2.52 %
Bacterial vaginosis	0	0.2 %	50	29.39 %	2.1 %
<i>Trichomonas vaginalis</i>	12 %	13 %	0	0.5 %	1.68 %
<i>C. trachomatis</i>	0	0	2.5	–	0

In the present study the commonest epithelial abnormality is ASCUS (4.62 %), followed by HSIL (3.36 %) and LSIL (2.10 %) which is similar to a study by Jha et al., and epithelial abnormalities are found to be ASCUS (3.19 %), LSIL (2.7 %) and HSIL (1.47 %), and Gaym et al., whose commonest epithelial abnormality was ASCUS (10.52 %) which was a combination of ASCUS and ASC-H. In our study, ASCUS was 6.3 %, followed by LSIL (5.15 %) and HSIL (4.36 %) (Table 4).

HIV infection primarily affects women during their reproductive years. The coexistence of reproductive tract infections (RTIs) in HIV is mainly acquired via heterosexual contact [23].

Vaginal infections, including Candida (yeast) vaginitis (2.52 %), bacterial vaginosis (2.1 %) and *T. vaginalis* (1.68 %), were commonly found in HIV-infected women in present study. No case of *Chlamydia trachomatis* was observed. Similar findings were noted in study done by Jha et al. where Candida vaginitis was (1.78 %) and *Trichomonas* was (0.5 %), and by Sharma A whose commonest finding was Candida vaginitis (34 %) followed by *T. vaginalis* (12 %).

Due to increased public awareness, proper treatment and proper follow-up ultimately decreases the risk of HIV transmission. The RTIs are suffered by both men and women, but their consequences are far more devastating and widespread among women. Among women, RTIs often go undiagnosed and untreated. It is a burden of asymptomatic disease, which is responsible for the frequent and severe long-term morbidity and in part for the persistence and spread of sexually transmitted diseases (STIs) in the community [2].

Maximum patients in present study had normal P/S (83.33 %) and 6.67 % showed erosion compared with Jha et al. 58.41 % normal, and 13.52 % showed erosion and Bagga had 32.4 % normal and 2.5 % erosion, suggesting that regular follow-up with Pap smear irrespective of normal PV/PS is must in HIV-positive women to rule out epithelial abnormality (Table 5).

Table 5 Epithelial cell abnormalities versus CD4 count

CD4 cell category (cells/cum ²)	Jha et al. [9] (n = 407; %)	Present study (n = 238; %)
>500	13.03	40
200–500	76.9	50
<200	10.07	10

Similar to previous studies, our study also got inconclusive results of effect of ART on cause of epithelial abnormality [24].

In the present study majority of the HIV-infected females (50 %) are having a CD4 count in the range of 200–500 cells/cum², while (40 %) are in the CD4 category greater than 500 cells/cum² and 10 % were having CD4 count less than 200 cells/cum². These findings were comparable with study done by Jha et al., showed 76.9 % in the range from 200 to 500 cells/cum² while (13.03 %) were in the category of >500 cells/cum².

HIV seropositivity and lower CD4 count are the strongest predisposing factors for the persistence of HPV.

The effect of immune function studies has demonstrated that CD4 count is a significant predictor for having or developing CIN [10, 20]. Study done by Amphan et al. had shown that CD4 cell count is a significant predictor for developing CIN [20, 21]; however, in our study we were unable to determine the effect on underlying pathology due to small sample size, and irregular follow-up. Among the epithelial cell abnormality ASCUS is commonest finding in our study. Eleven cases of ASCUS were seen which on microscopy showed squamous epithelial cells with increased nuclear-to-cytoplasmic ratio, along with hyperchromatic nuclei and irregular distribution of chromatin. HIV-positive females with ASCUS are advised repeat smear after 6 months.

Out of the 11 cases only 3 cases came for repeat Pap smear, out of which 2 reverted back to NILM, while 1 progressed to HSIL. One case out of 11 was unsatisfactory initially later on repeat smear is diagnosed as ASCUS.

Only 8 cases were HSIL. Only 3 came for follow-up. Repeat follow-up Pap was advised after 3 months, 3 out of which still showed the same finding, and thus colposcopy was advised. Microscopic squamous cells with increased nuclear-to-cytoplasmic ratio, with hyperchromatic nuclei with variation in size and shape, were observed. The chromatin is fine or coarsely granular. Cytoplasm is scanty and 1 among them was not advised colposcopic biopsy, and the remaining 2 were advised colposcopic biopsy, while both showed CIN2.

Only 4 cases were ASC-H. Microscopic squamous cells with increased nuclear-to-cytoplasmic ratio, with nuclear abnormality, i.e. hyperchromasia, irregular chromatin, abnormal nuclear shapes, were observed. The cytoplasm resembles metaplastic cells, thus confused with HSIL. No patient follow-up is seen.

LSIL consisted of only five cases. Microscopic squamous cells with increased nuclear-to-cytoplasmic ratio, coarse granular chromatin, perinuclear koilocytosis, i.e. sharp delineated clear perinuclear zone with a peripheral rim of densely stained cytoplasm, were observed. Out of the 5 cases only 1 case was diagnosed as unsatisfactory initially on follow-up diagnosed as LSIL. No patient follow-up till date was seen.

Only 2 cases of SCC were seen, both of which had bleeding per vaginum and low CD4 count. Microscopic dissociated single cells with nuclei are markedly increased in size. Nuclei also showed hyperchromatism, pleomorphism along with irregular nuclear membrane, and coarsely granular chromatin and scanty cytoplasm were seen. Presence of tadpole cells along with tumour diathesis was also observed.

Due to small study size, we are not able to comment on strategy authentically, but we can say that HIV-positive women should have Pap smear testing done regularly along with HPV testing. They should be educated and motivated to do Pap smear and HPV testing irrespective of CD4 count and ART.

Conclusion

The prevalence of Pap smear abnormalities in HIV-seropositive women is found to be 12.60 %. Progress of epithelial abnormality in HIV is independent of CD4 count, but incidence of epithelial abnormality is more with CD4 count <500. ART does not have any effect on the incidence of epithelial cell abnormality.

To achieve the millennium goal of decreasing mortality by cervical cancer, adequate screening of these HIV-positive women by Pap smear is necessary. To do this, developing proper infrastructure is a must [25, 26]. HIV-infected women with abnormal Pap smears are a population subset

with higher risk of significant cervical epithelial lesions, irrespective of severity of abnormal cervical smears [10].

Worth noting is an understanding of the true prevalence of precancerous lesions as we have studied with conventional Pap smear screening. As follow-up plays an important role in decreasing the morbidity and mortality, steps should be taken for proper health education, counselling of HIV-positive females for motivation to do regular follow-up Pap smear in HIV-positive females.

With high lost-to-follow-up rate, an appropriate interval of Pap smear screening could not be concluded from the present study. HIV-positive females should be motivated to do follow-up by Pap smear and colposcopic biopsy wherever advised to prevent cervical cancer. Facility of HPV co-testing is also needed along with Pap smear in HIV-infected women [27].

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Compliance with Ethical Standards

Conflict of interest Dr. Apeksha Madan has not received any research grants. Dr. Sunita Patil has not received a speaker honorarium from any company. Dr. Leena Nakate is a member of ethical committee in our college. Dr. Apeksha declares that she has no conflict of interest. Dr. Sunita Patil declares that he/she has no conflict of interest.

Research Involving Human Participants and/or Animals No animals were involved in this study. In cases, humans were involved.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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