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Impact of antiretroviral therapy on cervical pre-cancerous lesions: a prospective cohort study from a tertiary care institute in India

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Abstract

Introduction: Women living with human immunodeficiency virus (HIV) are at an increased risk for development of persistent human papillomavirus (HPV) infection, and expansion of precancerous lesions and invasive carcinoma of cervix. There is paucity of data from developing countries regarding HIV infection and its correlation with CD4+ counts.

Material and methods: A hospital-based, observational, prospective cohort study was conducted at the antiretroviral therapy (ART) center of tertiary referral institute in South India. The aim of the study was to analyze the cytological abnormalities in women living with HIV, and compare the differences between patients on and not on ART. A detailed history and complete general and systemic examination were performed, followed by Pap smear.

Results: The study included 228 women living with HIV, aged over 18 years, attending ART center OPD; 114 patients were on first-line ART for at least one year duration, and 114 were not on ART. In both the on ART and not on ART groups, the most commonly reported abnormal cytology report was inflammatory smear (36% and 25.4%) and bacterial vaginosis (9.6% and 10.5%), followed by low-grade squamous intra-epithelial lesion (16.7% and 14.9%). In high-grade squamous intra-epithelial lesion patients ($n = 8$), CD4+ counts were not found significantly different between those on and not on ART ($p = 0.25$).

Conclusions: The current study reflects the absence of differences between cytological abnormalities in women on ART and not on ART as well as the lack of protective effect with the former on squamous intra-epithelial lesion.

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Key words: HIV, squamous intra-epithelial lesions, antiretroviral therapy, CD4+ count.

Introduction

Indian sub-continent has the 3rd highest number of people living with human immunodeficiency virus (HIV), with an estimate of 2.5 million people being infected, showing maximum prevalence in the age range of 15-49 years [1]. HIV-positive women are at an increased risk of developing infections, such as human papillomavirus (HPV), which in turn is the most causative organism for development of pre-cancer-

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ous lesions and invasive carcinoma of cervix. The proximity of these two diseases highlights the need for understanding how HIV infection and its treatment with antiretroviral therapy (ART) may interact with cervical cancer [2].

The natural history of HPV infection is altered in persons infected with HIV, in whom there is an increased likelihood of persistent HPV infection [3], and higher risk of cervical dysplasia and cervical intra-epithelial neoplasm (CIN). This dual infection is mostly observed in the average age group of 30-40 years, indicating that HPV is more likely to be persistent in the setting of HIV infection, or that its reactivation may occur, increasing the chances of cervical cancer. The incidence of women with high-risk genotypes of HPV or with cervical pathology is more prevalent in HIV-negative women. Higher plasma HIV RNA levels and lower CD4+ counts have been associated with an increase in HPV incidence and cervical cytological abnormalities [4].

The high-rate of cervical diseases reported in HIV-infected women and the extended life expectancy due to better access to ART, have led to recommendations for aggressive screening and prompt treatment of cervical lesions. While few studies from India are available showing cervical smear abnormalities in HIV-infected, not much data are available comparing it with CD4+ counts, HIV viral load, and HPV DNA [5].

Table 1. Study population

Clinical findings	HIV cases on ART (n = 114)	HIV cases not on ART (n = 114)
Duration of HIV, months (mean)	72.12 (SD = 1.12)	57.26 (SD = 19.88)
Duration of antiretroviral therapy, months (mean)	57.05 (SD = 21.62)	N.A.
Intravenous drug abuse		
Yes	0	0
No	114	114
Smoking		
Yes	1	1
No	113	113
Menorrhagia		
Yes	17	22
No	97	92
Post-coital bleeding		
Yes	1	0
No	113	114
Oral contraceptives use		
Yes	15	15
No	99	99
Post-menopausal		
Yes	4	5
No	110	109

Material and methods

The present study was a hospital-based, observational, prospective cohort study conducted at an ART center of tertiary referral institute in South India. The aim of the study was to analyze the cytological abnormalities in women living with HIV, and to compare with the differences between those on and not on ART.

Study population consisted of women living with HIV, older than 18 years, who were registered at the ART center and under regular follow-up. All symptomatic HIV-positive females with AIDS defining criterion, pregnant women, patients on second-line ART or treatment failure, and cases with a past history of cervical dysplasia already under treatment, were excluded from the study.

Depending on ART administration, patients were divided into two groups: those on ART and not on ART. At our center, ART is routinely initiated when the CD4+ count falls below 350 cells/mm^3. After obtaining informed consent, a detailed history and complete general and systemic examination were done, followed by a Pap smear. Ectocervical smear sample was taken using Ayre spatula, and endocervix was sampled with cyto-brush. Both were transferred to glass slides, which were immediately fixed with 95% ethanol and ether mixture for 15 minutes. The slides were labelled and sent for pathology. Patients who were detected with any cervical cytological abnormality were then referred to gynecology department for further evaluation.

Statistical analysis

Quantitative data were represented with mean and standard deviation, and qualitative data as percentages. The primary outcome, i.e., cytological abnormalities, were represented with 95% confidence interval. Bivariate analysis was done using χ^2 and unpaired t-tests. Wherever data was not typical, non-parametric equivalent Mann-Whitney U test was used for statistical analysis. Statistical analysis was done with a Epi Info v. 3.5.1 software. A p-value of < 0.05 was considered statistically significant.

Results

The study included 228 women living with HIV, aged over 18 years, attending ART center OPD; 114 patients were on first-line ART for at least one year duration and 114 were not on ART. The mean duration of being on ART for the entire ART cohort was 6 years (72 months), and for those not on ART, it was 5 years and 6 months (57 months). One case in each group had a positive history of smoking, and fifteen cases in each group had a history of oral contraceptive usage. In all study population, only one patient from the ART group had a history of post-coital bleeding.

Table 2. Baseline variables

Baseline variables	HIV cases on ART (*n* = 114)	HIV cases not on ART (*n* = 114)	*p*-value
Mean age (years)	33.4 (SD = –7.5)	33.2 (SD = –8.8)	0.822
Mean age of menarche (years)	12.26 (SD = –1.6)	11.69 (SD = 1.7)	**0.013**
Parity, *n* (%)			
Nullipara	5 (4.4)	6 (5.3)	0.026
Primipara	7 (6.1)	13 (11.4)	
Multipara	102 (89.5)	95 (83.3)	
Baseline CD4+ count at diagnosis, *n* (%)			
< 350 cells/mm^3	86 (75.4)	None	**0.0001**
350-500 cells/mm^3	21 (18.4)	25 (21.9)	
> 500 cells/mm^3	7 (6.1)	89 (78.1)	
CD4+ counts at the time of study, *n* (%)			
< 350 cells/mm^3	21 (18.4)	None	**0.03**
350-500 cells/mm^3	25 (21.9)	45 (39.4)	
> 500 cells/mm^3	68 (59.6)	69 (60.5)	
Examination findings, *n* (%)			
Cervical erosion	16 (14.0)	21 (18.4)	0.673
Unhealthy cervix	10 (8.8)	8 (7.0)	
Vaginal discharge	30 (26.3)	31 (27.2)	
No abnormality	58 (50.9)	54 (47.4)	

Table 3. Cytological findings

Cytological findings	HIV cases on ART, *n* (%)	HIV cases not on ART, *n* (%)
Normal	30 (26.3)	38 (33.3)
ASCUS	0 (0)	4 (3.5)
Atrophic smear	2 (1.8)	4 (3.5)
Bacterial vaginosis	11 (9.6)	12 (10.5)
Chronic cervicitis	7 (6.1)	6 (5.3)
Inflammatory smear	41 (36.0)	29 (25.4)
LSIL	19 (16.7)	17 (14.9)
HSIL	4 (3.5)	4 (3.5)
Total	114 (100.0)	114 (100.0)
χ^2 = 12.198	***df* = 8, *p*-value = 0.14, contingency co-efficient = 0.225**	

ART – antiretroviral therapy, ASCUS – atypical squamous cells of undetermined significance, LSIL – low-grade squamous intraepithelial lesion, HSIL – high-grade squamous intraepithelial lesion

However, 17 cases in the ART group and 22 cases in the not on ART group had menorrhagia. No patient presented with a positive history of intravenous drug abuse (Table 1). In our study, none of the women enrolled had ever undergone a Pap smear screening prior to the study. The baseline comparison of patients on ART versus those not on ART is demonstrated in Table 2. Both the groups were equally matched in terms of population demographics, such as mean age, parity, and clinical examinations findings. As expected, the CD4+ counts were significantly different between the two groups.

On evaluation of cytological abnormalities between the two groups of patients (Table 3), the most commonly reported cytology report was inflammatory smear and bacterial vaginosis, followed by low-grade squamous intra-epithelial lesion (LSIL). There was no statistically significant association between the two groups with respect to cytological findings (*p*-value = 0.143). No cases of invasive cervical cancer (ICC) were observed.

A sub-group analysis of patients with squamous intraepithelial lesions (SIL) [i.e., LSIL and high-grade squamous

Table 4. High-grade squamous intraepithelial lesion (HSIL) and low-grade squamous intraepithelial lesion (LSIL)

Parameters	HSIL			LSIL		
	HIV cases on ART (n = 4)	HIV cases not on ART (n = 4)	p-value	HIV cases on ART (n = 19)	HIV cases not on ART (n = 17)	p-value
	mean ± SD			mean ± SD		
Age (years)	35.00 SD = 5.00	38.50 SD = 5.97	0.38	30.42 SD = 5.79	31.35 SD = 7.56	0.66
Age of first menarche (years)	11.5 SD = 2.38	10.25 SD = 0.50	0.38	12.74 SD = 1.32	12.00 SD = 1.73	0.26
CD4+ count baseline (cells/mm^3)	229.75 SD = 200.49	533.75 SD = 191.23	0.052	222.32 SD = 23.81	614.65 SD = 200.19	**0.01**
CD4+ count latest (cells/mm^3)	275.75 SD = 122.15	396.50 SD = 21.70	0.25	375.17 SD=142.1	493.18 SD = 194.53	**0.04**

intra-epithelial lesion (HSIL) patients] was performed (Table 4). In HSIL sub-group (n = 8), CD4+ counts were found not significantly different between patients on or not on ART.

Discussion

The increasing use of ART in the previous decade has played a pivotal rale in improving clinical condition and quality of life of people living with HIV/AIDS. Various studies have speculated that increasing level of CD4+ counts and, therefore, immunological status would help in better detection of HPV infection in HIV-infected women. At the same time, the real evidence from the developed countries does not suggest such evident reduction in the severity and burden of cervical diseases since the advent of ART [6-8]. Our study reflects the absence of difference between the cytological abnormalities in women on ART and those not on ART as well as the lack of protective effect with the former on SIL. An explanation for this may be the persistent HPV-related accumulative oncogenic alterations in the cells of squamocolumnar junction of the cervix, resulting in CIN or SIL, which may not be cleared/reversed by the changing nature of immunological status delivered by ART in the short-term.

High HPV load in HIV-positive women is associated with a 10-fold increased risk of CIN in severe immunosuppression [9]. It has been speculated that the persistence of HPV is related to the immune status, reflected by two-fold increase in the prevalence of SIL, with CD4+ count less than 200 cells/mm^3 [10]. Similarly, low CD4+ count levels are associated with abnormal Pap smear results [11]. In our study, a statistically significant association was found between LSIL in both the groups with respect to baseline and latest CD4+ counts; however, there was no association found with HSIL lesions, most likely due to very small sample size.

Few studies have associated the benign lesions of cervix with HIV status of women, and even fewer have compared women on the basis of their ART status. With the advent of ART therapy and long survival of HIV-positive women, these patients are likely to suffer from the above-mentioned co-infections, for which they need to be diagnosed and treated accordingly. Apart from dysplastic changes and benign lesions of the cervix, 30 out of 114 HIV-positive women (26.3%) on ART and 38 out of 114 HIV-positive women (33.3%) not on ART were found to have normal cervical cytology. However, none of the results was found statistically significant, with a Pearson χ^2 of 12.198 and p-value of 0.143.

Data demonstrating any impact of ART on progression of disease remain inconclusive, providing conflicting results. While it is possible that restored immune competence due to ART may prevent the progression of disease, it is likely that progressive lesions demonstrate slow oncogenic changes due to persistent HPV infection, which are possibly unaltered by the changes in the immune status attained due to ART. Accurate analysis and interpretation of studies is difficult, as they differ in their markers of patient immunological status (e.g., CD4+ counts, duration of being HIV-infected) and treatment characteristics (e.g., duration of being on ART, adherence to ART, and effectiveness of ART).

In 2000, the International Collaboration on HIV and Cancer has published the incidence estimates of all cases of ICC mainly in developed nations in the pre-ART and post-ART eras, and revealed no difference in the ICC incidence rates [12]. While the developing world carries a disproportionate burden of the morbidity and mortality associated with cervical cancer and HIV/AIDS, most of the studies on the impact of ART on cervical cancer have been conducted and reported from industrialized nations [13, 14]. In these settings, a better and more comprehensive understanding of the impact of ART on cervical cancer in HIV-infected women is mandatory not only from an academic and scientific perspectives, but also from a resource allocation and program implementation point of view, as due to ART, HIV-infected women are now starting to live longer in a moderately immunocompetent state.

A drawback of the current study is its cross-sectional nature that prevents a longitudinal evaluation of natural history of cytological abnormality in women living with HIV. Furthermore, due to financial constraints, HPV testing was not done, which would provide some valuable insights into these patients. A prospective study investigating long-term

evolution of these lesions and their determinants is needed to further guide policy decisions.

Conclusions

The present study reinforces the fact that women living with HIV should be followed up more closely for various gynecological conditions, with screening for dysplastic lesions during their initial visit in ART clinic becoming a part of the routine evaluation. An initiation of ART should not entail a fake sense of protection for cytological abnormality of cervix.

Disclosures

1. Institutional review board statement: The study was reviewed by the Ethics Committee of the Armed Forces Medical College, Pune (approval number: IEC/AFMC/16/23).
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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