Original Article

Comparative study of preinvasive and invasive lesions of the cervix in HIV-positive and HIV-negative women

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ABSTRACT

Background: Evidence suggests that Human Immunodeficiency Virus (HIV) infection is a risk factor for preinvasive and invasive lesions of cervix but confusion regarding pathogenesis and progression of cervical neoplasia in HIV-positive women still prevails. **Aims:** To find the incidence of cervical neoplasia in HIV positive and HIV-negative women and to study the impact of CD4 counts, duration of HIV infection, and treatment with highly active antiretroviral therapy (HAART) on the incidence of cervical lesions in HIV positive women. **Materials and Methods:** It was an observational case control study carried over a period of one year at the Department of Obstetrics and Gynaecology and Department of Medicine, King George Medical University, Lucknow. Cases were HIV-positive women and controls were HIV negative women. Those with previous diagnosis or treatment for cervical neoplasia, history of total hysterectomy or coexistent immunosuppressive conditions were excluded. All subjects had cervical screening by Pap smear. Colposcopy and cervical biopsy were done if indicated. **Statistical Analysis Used:** Chi square test, univariate, and multivariate analysis. **Results:** The incidence of cervical lesions in HIV-positive women (159.66 per 1000 screened women) was higher compared to HIV-negative women (15.15 per 1000 screened women) ($P < 0.001$). CD4 counts less than 500/mm^3 were associated with an increased incidence of cervical neoplasia ($P < 0.00$I). The incidence of cervical lesions in HIV-positive women on HAART was 16.16% as compared to 15% in HIV-positive women not on HAART. Duration of HIV infection more than 2 years was associated with an increased incidence of cervical lesions in univariate analysis ($P < 0.001$). **Conclusions:** Seropositivity is associated with an increased incidence of cervical lesions. This risk is further enhanced by CD4 counts less than 500/mm^3 and duration of HIV infection of more than two years.

Key words: CD4 counts, cervical neoplasia, CIN, cervical lesions, HAART, HIV infection, HIV negative, HIV positive

INTRODUCTION

Benign and malignant lesions of the cervix are major causes of morbidity and mortality in females worldwide.

The Human Papilloma Virus is the major etiologic agent in the development of cervical cancer and its natural history of infection is altered in women infected with Human Immunodeficiency Virus (HIV). There is growing evidence that suggests HIV infection as a risk factor for preinvasive and invasive lesions of cervix. A study carried out by Peter Memiah *et al.*(2012)[1] on women attending the Nazareth Hospital Antiretroviral Therapy (ART) clinic showed the role of HIV-induced immunosuppression in the pathogenesis of cervical abnormalities and precancerous cervical lesions. Another study by Dr. B Clarke (2002)[2] suggested that the more aggressive behavior of cervical neoplasms in HIV-positive women is because of an accelerated progression via the microsatellite instability pathway, whereas the pathogenesis in HIV-negative women involved loss of heterozygosity. The confusion regarding the pathogenesis and progression of cervical neoplasia in HIV-positive women still prevails. Hence, the present study was planned.

The aims and objectives of present study were to study the impact of CD4 counts, duration of HIV infection, and treatment with highly active antiretroviral therapy (HAART) on the incidence of cervical lesions in HIV positive women.

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MATERIALS AND METHODS

It was an observational case control study conducted over a period of one year in the Department of Obstetrics and Gynaecology in collaboration with the Department of Medicine and Integrated Counselling and Testing Centre (ICTC) of King George Medical University, Lucknow. Subjects were recruited after written informed consent. Institutional ethical clearance was taken. Confidentiality of cases was maintained. The cases included 119 HIV-positive women in stable general condition attending the Department of medicine. Those with previous diagnosis or treatment for cervical neoplasia, history of total hysterectomy or coexistent other immunosuppressive conditions (non-Hodgkin's lymphoma, Kaposi's sarcoma) or immunosuppressive therapy were excluded. Controls included 132 HIV-negative women in stable general condition attending the department of Obstetrics and Gynaecology. A detailed history was taken to record demographic parameters, that is, age, parity, and religion. All women had cervical cytology by Pap smear. Colposcopy and cervical biopsy were done if indicated. The histopathology reports were obtained. For the purpose of this study, histopathology reports showing cellular atypia, cervical intraepithelial neoplasia (CIN) I, CIN II, CIN III, and cervical carcinoma were named cervical neoplasia. Statistical analysis was done using Chi square test, univariate, and multivariate analysis.

RESULTS

The observations were made on 119 HIV-positive women (cases) and 132 HIV-negative women (controls). The observations of the study showed that cases and controls were matched in terms of parity, religion, contraceptive method used, and tobacco intake as shown in Table 1. Majority of cases (73.1%) and controls (59.8%) were below 40 years of age. Among the various risk factors for cervical neoplasia, the onset of sexual life before 16 years of age was significantly ($P < 0.001$) higher in cases (34.45%) as compared to controls (14.39%).

The incidence of cervical lesions in HIV-positive women (159.66 per 1000 screened women) was higher compared to HIV-negative women (15.15 per 1000 screened women) with statistically significant difference ($P < 0.001$). HIV infection was independently associated with an increased incidence of cervical neoplasia in the univariate analysis ($P < 0.001$) as shown in Table 2. In multivariate analysis, the odds of cervical neoplasia were more than unity for HIV seropositivitiy, although it was not significantly associated ($P = 0.144$) with the outcome as shown in Table 3.

The Chi square test did not show any significant correlation between incidence of cervical neoplasia and CD4 counts below 500/mm^3 ($P = 0.173$). Univariate analysis showed that CD4 counts less than 500/mm^3 were independently associated with an increased incidence of cervical neoplasia ($P < 0.00I$) as shown in Table 2. The odds of cervical neoplasia were more than unity for CD4 counts <500/mm^3 in multivariate analysis although it was not significantly associated ($P = 0.207$) with the outcome [Table 3].

The incidence of cervical lesions in HIV-positive women on HAART was 16.16% as compared to 15% in HIV-positive women not on HAART, the difference not being statistically significant. The univariate analysis did not show any significant correlation between incidence of cervical

Table 1: Comparison of demographic factors in cases and controls

Risk factors	Cases (HIV positive) *n*=119		Controls (HIV negative) *n*=132		*P* value
	Number	%	Number	%	
Age (years)					
20-39	87	73.1	79	59.8	0.027
≥40	32	26.9	53	40.2	
Age at first intercourse					
<16	41	34.45	19	14.39	0.001
Parity					
0	12	10.08	11	8.33	0.073
1	18	15.12	17	12.88	
2	37	31.09	37	28.03	
3	17	14.28	36	27.27	
4	20	16.80	10	7.58	
5	11	9.24	12	9.1	
>5	4	3.36	9	6.81	
Tobacco intake					
Present	8	6.72	8	6.06	0.830
Religion					
Hindu	98	82.35	117	89.39	0.108
Muslim	21	17.65	14	10.60	

HIV: Human immunodeficiency virus. The above table shows that cases and controls are matched with respect to parity, tobacco intake, and religion

Table 2: Univariate assessment of association of cervical neoplasia with different clinical variables (*N*=251)

Variable	Total	No. with cervical neoplasia (*n*=21)	% of total	Significance
HIV				
Negative	132	2	1.5	$\chi^2 = 17.047$;
Positive	119	19	16.0	$P<0.001$
CD4				
No HIV or CD4 >500	153	4	I2.5	$\chi^2 = 18.514$;
CD4 <500	94	17	I8	$P<0.001$
HAART				
No disease or no HAART	152	5	3.3	$\chi^2 = 12.957$; $P<0.001$
On ART	99	16	16.2	
Duration of disease				
No or <2 years	179	7	3.9	$\chi^2 = 16.161$;
2 years	72	14	19.4	$P<0.001$

HAART: Highly active antiretroviral therapy, HIV: Human immunodeficiency virus. The above table shows that the independent variables: HIV infection, assumed duration of HIV infection, and CD4 counts <500/mm$^{[3]}$ are all associated with an increased incidence of cervical neoplasia, whereas, HAART does not seem to affect the incidence of cervical neoplasia

Table 3: Binary logistic regression-multivariate analysis

	B	S.E.	Wald	df	Sig.	Exp (B)
Step 1(a)						
Religion	0.962	0.660	2.124	1	0.145	2.617
Age >40 years	2.300	0.650	12.519	1	0.000	9.973
Parity	0.108	0.601	0.032	1	0.857	1.114
HIV infection	1.775	1.215	2.134	1	0.144	5.902
Duration of disease	0.845	0.649	1.697	1	0.193	2.329
HAART	−0.331	0.806	0.168	1	0.682	0.719
CD4 count	1.112	0.882	1.591	1	0.207	3.041
Age at first intercourse	0.327	0.576	0.322	1	0.571	1.386
Barrier	−0.273	0.661	0.171	1	0.679	0.761
Tobacco	0.251	0.973	0.066	1	0.797	1.285
Constant	−5.805	1.061	29.932	1	0.000	0.003

HAART: Highly active antiretroviral therapy, HIV: Human immunodeficiency virus. Variable(s) entered on step 1: Religion, Age, Parity, HIV, Duration of Disease, HAART, CD4 count, Age at first intercourse, Barrier, Tobacco. The above table shows that age >40 years is the only variable independently associated with increased incidence of cervical neoplasia. The odds are more than unity for HIV infection and CD4 counts although the association is not statistically significant

neoplasia and treatment with HAART as shown in Table 2. The results of the multivariate analysis showed a negative trend toward incidence of cervical lesions in HIV-positive women on HAART thereby indicating a possible protective effect of HAART against cervical lesions although larger studies are required to confirm this [Table 3].

In the present study, 58.82% of HIV-positive women were diagnosed within the last two years. Duration of HIV infection more than two years was independently associated with an increased incidence of cervical lesions in the univariate analysis ($P < 0.001$) as shown in Table 2. The multivariate analysis did not show a significant correlation ($P = 0.193$) between duration of HIV infection of more than two years and incidence of cervical neoplasia [Table 3].

DISCUSSION

The age-standardized cervical cancer incidence ranges from 9 to 40 per 100,000 women in various regions of India (Sankaranarayanan *et al*., 2008).[3] The estimated number of new cases of cervical cancer in India was 90,708 in 2007. In the present study, the incidence of cervical lesions among HIV positive females was 159.66 per thousand women screened compared to 15.15 per thousand women screened in controls. This difference was statistically significant ($P < 0.001$). The higher incidence in the controls, over and above that of general population could be explained by the fact that our controls were recruited from the symptomatic women presenting to the hospital. In the univariate analysis also, HIV infection was associated with a significantly higher incidence of cervical neoplasia ($P < 0.001$). Ellerbrock TV (2000)[4] reported a significantly higher incidence ($P < 0.001$) of squamous intraepithelial lesions in socio-demographically similar HIV-infected women (8.3 cases per 100 person-years) than uninfected women (1.8 cases per 100 person-years).

The multivariate analysis in the present study showed that the odds of cervical neoplasia were more than unity for HIV infection but the association was not statistically significant. La Ruche G (1998)[5] reported that in multivariate analysis, both low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL) were associated with HIV-1 infection. Massad LS (1999)[6] found that HIV infection was associated with increased incidence of abnormal cervical cytology in a multivariate assessment. Moscicki AB (2000)[7] showed that HIV infection was a significant risk factor for development of squamous intraepithelial lesion (SILs) in multivariate analysis.

Women infected with HIV are monitored with frequent CD_4 count and viral load assessment as they are important prognostic factors in disease progression. Delmas MC (2010)[8]compared HIV-positive women with CD4 cell counts above 500/mm^3 and those below 200/mm^3 and found a two-fold increase in both prevalence and incidence of SIL in women with CD4 counts less than 200/mm^3. Peter Memiah (2012)[1] also reported that HIV-positive women with CD4 counts less than 200/mm^3 were 1.6 times more likely to have cervical precancerous lesions compared to those with CD4 count more than 200/mm^3 Swende TZ (2012)[9] reported that a CD4 lymphocyte count less than 200 cell/mm^3 was significantly associated with cervical SIL. In the present study, univariate analysis showed that CD4 count less than 500/mm^3 was associated with significantly higher incidence of cervical neoplasia compared to CD4 counts more than 500/mm^3 or absence of HIV infection. This fact supports the role of immunosuppression contributing to increased incidence of cervical neoplasia in HIV positive women.

The HAART has been evaluated as an immunomodulator in HIV-positive women with cervical lesions. De Vuyst (2008)[10] found no beneficial effect of HAART on the natural history of intraepithelial lesions of cervix in HIV positive women. Adler DH (2010)[11] found that even as the partial immune reconstitution afforded by HAART might be expected to decrease susceptibility to human papillomavirus (HPV) infection and cervical disease, the local effects of improved immunosurveillance on the cervix are uncertain and the increased longevity of patients on HAART may increase risk of exposure to HPV and provide the time required for progression of cervical disease. However, in the present study, the treatment with HAART did not seem to affect development of cervical lesions in HIV positive women. 83.2% of HIV-positive women were receiving HAART at the time of recruitment. SIL was diagnosed in 16.16% of

these women (HAART group) and in 15% of women not receiving HAART. This difference was not statistically significant. Therefore, the effect of HAART on incidence and progression of cervical neoplasia needs to be studied further to arrive at definitive results.

The association between duration of HIV infection and incidence of cervical lesions has not been studied extensively. Chalermchockcharoenkit A (2011)[12] found a higher incidence of atypical squamous cells of undetermined significance (ASCUS) and higher lesions with an increase in assumed duration of HIV infection. In our study, univariate assessment of cervical neoplasia with different demographic and clinical variables showed that duration of HIV infection of more than two years was associated with significantly increased incidence of preinvasive and invasive lesions of cervix ($P < 0.001$).

The results of the present study suggest that it is imperative to screen HIV-positive women for cervical neoplasia as soon as they are diagnosed with HIV infection and further screenings should be performed at more frequent intervals.

CONCLUSION

Human Immunodeficiency Virus infection is associated with an increased incidence of cervical neoplasia. This risk is further enhanced by CD4 counts less than 500/mm^3 and HIV infection of more than two years duration. Treatment with HAART did not seem to affect the incidence of cervical neoplsia in HIV positive women. Considering the current knowledge, HIV-positive women must be counseled and screened for cervical neoplasia as soon as they are diagnosed with HIV infection adhering to Centers for Disease Control and Prevention (CDC) guidelines.[13]

REFERENCES

1. Memiah P, Mbuthia W, Kiiru G, Agbor S, Odhiambo F, Ojoo S, *et al*. Prevalence and Risk Factors Associated with Precancerous Cervical Cancer Lesions among HIV-Infected Women in Resource-Limited Settings. AIDS Res Treat 2012;2012:953743.
2. Clarke B, Chetty R. Postmodern cancer: The role of human immunodeficiency virus in uterine cervical cancer. Mol Path 2002;55:19-242.
3. Thulaseedharan JV, Malila N, Hakama M, Esmy PO, Cheriyan M, Swaminathan R, *et al*. Socio Demographic and Reproductive Risk Factors for Cervical Cancer - a Large Prospective Cohort Study from Rural India. Asian Pac J Cancer Prev 2012;13:2995.
4. Ellerbrock TV, Chiasson MA, Bush TJ, Sun XW, Sawo D, Brudney K, *et al*. Incidence of cervical squamous intraepithelial lesions in HIV -infected women. JAMA 23;283:1031-74.
5. La Ruche G, Ramon R, Mensah-Ado I, Bergeron C, Diomande M, Sylla-Koko F, *et al*. Squamous intraepithelial lesions of the cervix, invasive cervical carcinoma, and immunosuppression induced by human immunodeficiency virus in Africa. Dyscer-CI Group. Cancer 1998;82:2401-8.
6. Massad LS, Riester KA, Anastos KM, Fruchter RG, Palefsky JM, Burk RD, *et al*. Prevalence and predictors of squamous cell abnormalities in Papanicolaou smears from women infected with HIV-l. Women's Interagency HIV Study Group. J Acquir Immune Defic Syndr 1999;21:33-41.
7. Moscicki AB, Ellenberg JR, Vermund SH, Holland CA, Darragh T, Crowley-Nowick PA, *et al*. Prevalence of and risks for cervical human papillomavirus infection and squamous intraepithelial lesions in adolescent girls: Impact of infection with human immunodeficiency virus. Arch Pediatr Adolesc Med 2000;154:127-34.
8. Delmas MC, Larsen C, van Benthem B, Hamers FF, Bergeron C, Poveda JD, *et al*. Cervical squamous intraepithelial lesions in HIV -infected women: Prevalence, incidence and regression. European Study Group on Natural History of HIV Infection in Women. AIDS 2000;14:1775-84.8.
9. Swende TZ, Ngwan SD, Swende LT. Prevalence and risk factors for cervical squamous intraepithelial lesions among women infected with HIV-l in Makurdi, Nigeria. Int J Womens Health 2012;4:55-60.
10. De Vuyst, Lilo F, Broutet N, Smith JS. HIV, human papillomavirus, and cervical neoplasia and cancer in the era of highly active antiretroviral therapy. Eur J Cancer Prevo 2008;17:545-54.
11. Adler DH, The impact of HAART on HPV-related cervical disease. Curr HIV Res 2010;8:493-7.
12. Chalermchockcharoenkit A, Chayachinda C, Thamkhantho M, Komoltri C. Prevalence and cumulative incidence of abnormal cervical cytology among HIV -infected Thai women: A 5.5-year retrospective cohort study. BMC Infect Dis 2011;11:8.
13. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually Transmitted Diseases Treatment guidelines 2010. MMWR Recomm Rep 2010;59:1-110.

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