Colposcopic Study of Lower Genital Tract Infections in HIV-Positive Women on Antiretroviral Therapy

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Abstract

Aims and Objectives To study the colposcopic findings and prevalence of lower genital tract infections in HIV-positive women on anti-retroviral therapy. To find correlation between colposcopic finding, m RNA HPV and cytology of lower genital tract infections in HIV-positive women on anti-retroviral therapy.

Materials and Methods The present prospective observational study was conducted in the Department of Obstetrics and Gynaecology, Netaji Subhash Chandra Bose Medical College, Jabalpur, from 1 June 2013 to 31 October 2014. The data of the present study was recorded into computer and after proper validation, error checking, coding and decoding, the data was compiled and analysed using the SPSS Windows. Appropriate univariate and bivariate analysis were carried out using the Student's t test and two-tailed Fisher exact test or Chi-square test for categorical variables.

Results and Conclusion The present study concludes that the prevalence of lower genital tract infections is 25.3 % in HIV-positive women on anti-retroviral therapy. It revealed that 35 HIV-positive women on anti-retroviral therapy who were screened for m HPV RNA test, one came out to be positive (i.e. 2.8 %); thus, it can be said that there is an increased clearance of oncogenic HPV types in HIV-positive women on anti-retroviral therapy.

Keywords HIV · Human papillomavirus · Antiretroviral therapy · Lower genital tract infections · Colposcopy

Introduction

The global burden of reproductive tract infections is enormous and of a major public health concern, particularly in developing countries where reproductive tract infections are endemic. The World Health Organization estimates that each year, there are over 333 million new cases of curable sexually transmitted infections [1]. Reproductive tract infections, excluding human immunodeficiency virus (HIV), constitute the second major cause of disease burden (after maternity-related causes) in young adult women in developing countries [1]. Reproductive tract infections cover three types of infections: sexually transmitted infections; infections that result from overgrowth of organisms normally present in the reproductive tract; and infections associated with medical procedures including abortion and insertion of intra-uterine devices [2, 3]. Reproductive tract infections entail a heavy toll on women and if untreated can cause serious consequences of infertility, ectopic pregnancy, cervical cancer, menstrual disturbances, pregnancy wastage and low-birth-weight babies [1]. The presence of reproductive tract infections, especially ulcer-causing STIs, can enhance the acquisition and transmission of the human immunodeficiency virus [4].

Cervical cancer is usually the result of sexually transmitted infection, and human papilloma virus is the causative agent. It is the commonest reproductive tract malignancy [5]. In contrast to most other cancers, it is common below the age of 50 years and is therefore an important cause of premature death [6]. Other sequelae of reproductive tract infections also have enormous impact on the population [2, 3].

HIV-positive women are at higher risk of developing reproductive tract infections compared with HIV-negative women.

Large observational studies involving HIV-positive women have demonstrated a strong and consistent

association between co-infection with HIV, HPV and cervical intra-epithelial lesions. It is therefore important for clinicians to screen patient who are HIV-positive women routinely for reproductive tract infections and cervical intra-epithelial lesions. Most common types of lower genital tract infections and disease are trichomoniasis, bacterial vaginosis, herpes, candidiasis, gonorrhoea, syphilis, chlamydial infections, cervical intra-epithelial lesion due to HPV, genital warts, vulvar intra-epithelial neoplasia, vaginal intra-epithelial neoplasia and anal intra-epithelial neoplasia. Cervical cytological examination to detect precancerous lesions is the most often used screening method amongst women, including those with HIV infection.

According to the women's interagency HIV study report, women who were taking anti-retroviral therapy had higher rates of regression than progression of cervical intra-epithelial lesions and also revealed improvement in HPV infection CD4+ cell count and pap status. This is plausible because anti-retroviral therapy reverses immunodeficiency as measured by CD4 cells counts, IL-8 and IL-1 levels and reduces HIV virus load [7].

Justification

The appropriate approach for screening and treatment of lower genital tract infections in HIV-positive women is subject of debate because of an incomplete understanding of their natural history in this patient population, especially with the advent of anti-retroviral therapy.

The present study was conducted to find out the impact of anti-retroviral therapy on lower genital tract infections and cervical intra-epithelial lesions.

Materials and Methods

The present prospective observational study was conducted in the Department of Obstetrics and Gynaecology, NSCB medical college, Jabalpur, from 1 June 2013 to 31 October 2014. The sample size was 75 which was calculated by following formula:

$$n = z^2(p \cdot q) / d^2$$

where $z = 1.96$ for 95 % confidence interval, p = assumed probability (prevalence), $q = 1 - p$, d = marginal absolute error = 10 %.

Inclusion Criteria

- All women above 18 years, who are sexually active, HIV positive and on anti-retroviral therapy.

Exclusion Criteria

1. Women with frank invasive carcinoma cervix (with visible growth in cervix).
2. Women with bleeding per vaginum.

Methodology

HIV-positive women registered with ART in medical college centre were counselled for gynecology examination and testing in Department of Gynecology. A total of 108 HIV-positive women were counselled, and out of these, 75 women gave consent for examination and testing. In the Gynecology outpatient department, they were explained the procedure and informed consent was taken. These women were subjected to the screening for lower reproductive tract infections, i.e. pap smear, wet mount, m HPV RNA test and colposcopy. Colposcopic examination of the perianal region and vulva was done. A self-retaining Cusco's speculum was applied. With the help of cytobrush, sample from ectocervix and endocervix was taken and placed in the m HPV RNA vial and was sent by courier to Cure Health Diagnostics Pvt. Ltd (Free samples were issued for the research work). After m HPV RNA sampling, wet mount slides were prepared and examined in side laboratory, pap smear was taken, fixed with 95 % ethanol, and slides were sent to Pathology Department of our institute for examination. Cervix was cleaned with saline swab. Ectocervix and vagina was examined under green filter. Freshly prepared 5 % glacial acetic acid solution was applied on the ectocervix.

As per IFCPC 2011 classification, findings were noted, and adequacy and inadequacy of the squamo-columnar junction were noted as transformation zone T1, T2, T3 [8].

If pap and VIA was negative, women were sent back and advised to come after 6 months for routine screening. If there was presence of VIA positive lesion, then the cervix was divided into four quadrants by an imaginary line passing through the centre from 6'o clock to 12'o clock position and from 3'o clock to 9'o clock position. Colposcopic examination of each quadrant was done in a clockwise direction starting from right upper quadrant (from examiner side) [9], and findings were documented in equations type.

Results

Demographic Results

In the present study, 38.7 % of the study population belong to 20–30 years of age group, and amongst 18 positive cases

with the minor colposcopic findings, 7 cases belong to the 20–30 years of age group. The presence of one major colposcopic finding (vulval lesion) was also from this age group.

Out of total, 54.5 % women were from urban area, 18 positive cases with minor colposcopic findings (lower genital tract infections), 10 cases (53.5 %) belong to rural population.

97.3 % of the studied group was Hindu by religion, and 100 % of all cases which showed minor and major colposcopic changes were Hindu by religion.

53.3 % of the studied group were illiterate, and 61.3 % of the husbands of these women were illiterate. Out 18 positive cases with minor colposcopic findings (lower genital tract infections), 9 cases (50 %) were illiterate. This observation was found to be statistically significant ($p = 0.005$).

80 % of the studied group were housewives by occupation. All cases which showed minor and major colposcopic changes were housewives by occupation.

57.3 % of the husbands of the studied population were driver by occupation. Out of 18 cases with the minor colposcopic changes (lower genital tract infections), 50 % husbands were driver by occupation and 1 with major colposcopic change (vulval lesion) was also driver by occupation. This was found to be statistically significant ($p = 0.01$) (Fig. 1).

Out of 18 positive cases with minor colposcopic findings (lower genital tract infections), 66.7 % had more than 10 years of marital life.

Out of 18 positive cases with the minor colposcopic findings (lower genital tract infections), 77.5 % were multipara.

62.7 % of the studied group came with the complaint of white discharge, and there were 33.4 % cases who showed minor colposcopic findings (lower genital tract infections).

There were four cases with abdominal pain and one case with the burning micturition, and all showed minor colposcopic findings (lower genital tract infections). This was found to be statistically significant ($p < 0.001$) (Fig. 2).

Out of 75 cases studied, 19 cases were VIA positive. Amongst this, 18 positive cases showed minor colposcopic findings (lower genital tract infections) and one case showed major colposcopic finding (vulval lesion excoriation) (Table 1).

Out of 18 positive cases with the minor colposcopic findings (lower genital tract infections), 83.4 % had CD₄ count between 200 and 499 cell/cu mm. One case with major colposcopic finding had CD₄ count of <200 cells/cu mm. This was found to be statistically significant ($p < 0.001$) (Table 2).

Fig. 1 Colposcopic changes were seen more in those women whose husbands were driver by occupation

Fig. 2 Studied group with complain of white discharge showed colposcopic changes

Table 1 Association of VIA with the colposcopic findings (IFCPC 2011 classification)

VIA	Normal	Major colposcopic findings	Minor colposcopic findings	Total
Negative	56 100 %	0	0	56
Positive	0	1 100 %	18 100 %	19
Total	56	1	18	75

$\chi^2 = p < 0.0001$, Fisher exact test = $p < 0.0001$

Out of 18 cases with the minor colposcopic findings (lower genital tract infections), two cases showed ASCUS on pap smear ($p < 0.001$) (Table 3).

Table 2 Association of CD4 count with the colposcopic findings (IFCPC2011 classification)

CD ₄ count (cells/cumm)	Normal	Major colposcopic findings	Minor colposcopic findings	Total
<200	0	1 100 %	2 11.2 %	3
200–499	12 21.4 %	0	15 83.4 %	27
>500	44 79.6 %	0	1 5.4 %	45
Total	56	1	18	75

$\chi^2 = p < 0.0001$, Fisher exact test = $p < 0.001$

Table 3 Association of pap smear with the colposcopic findings (IFCPC 2011 classification)

Pap smear	Normal	Major colposcopic findings	Minor colposcopic findings	Total
Normal	55	0	16	71
Ascus	1	1	2	4
Total	56	1	18	75

$p < 0.0001$, Fisher exact test = $p < 0.0001$

Fig. 3 One case was m HPV RNA positive in women on HAART

Out of 18 cases with minor colposcopic findings (lower genital tract infections), 11 cases had received HAART for <1 year. This finding was found statistically significant ($p = 0.003$).

Out of 75 cases studied, m HPV RNA oncotest was carried out for 35 cases, in which one case was found out to be positive (Fig. 3).

In the present study conducted, prevalence of various lower genital tract infections was: 1.3 % HPV, 5.5 % candidiasis, 16.6 % trichomoniasis and 76.6 % non-specific cervicitis.

Discussion

Relation of Minor Colposcopic Changes (Lower Genital Tract Infections) with Presenting Complaints (Fig. 2)

In the present study, 62.7 % presented with the complaint of white discharge and 14.6 % with itching over private parts.

Amongst these, 55.6 % with the complaint of white discharge and itching over private parts had minor colposcopic changes (lower genital tract infections).

22.2 % women presented with abdominal pain and 5.6 % women with burning micturition had minor colposcopic changes (lower genital tract infections).

One case (5.5 %) presented with tcurdy white discharge showed minor colposcopic changes and wet mount positive for candidiasis.

Itching over private parts was present in three cases (16.6 %) with trichomoniasis.

Abdominal pain, burning micturition and other complaints were found to be statistically significant ($p = 0.04$).

Association of Colposcopic Findings (Lower Genital Tract Infections) with Visual Inspection with Acetic Acid (Table 1)

Out of 75 cases studied, there were total 18 cases who had minor colposcopic changes and one case with major colposcopic change, and rest were found to be negative.

This observation was found to be statistically significant ($p < 0.0001$).

In the study group, 18 cases with the minor changes was found in colposcopy had lower genital tract infections (fine acetowhite lesion) and one case with vulval lesion (excoriation and erosion) have major change.

In the study group, there were 26.4 % cases who were VIA positive, but there was no CIN lesion detected.

CD4 Count and its Association with the Colposcopic Findings (Table 2)

In the present study, 4 % of the studied population had CD4 count of <200 cells/cu mm, 36 % had CD4 count of 200–499 cells/cu mm and 60 % cases had more than 500 cells/cu mm.

In Susan Cu-Uvin et al. study [10], there were 17 % cases with CD4 count of <200 cells/cu mm, 50 % cases with the CD4 count of 200–499 cells/cu mm and 32 % cases with the CD4 count with more than 500 cells/cu mm.

One case with major colposcopic change (vulval lesion) showed CD4 count of <200 cells/cu mm.

This was found to be statistically significant.

In Susan Cu Uvin et al. [10] study, there was no statistically significant difference in the prevalence of lower genital tract infections by CD4 count, except for a higher prevalence of trichomoniasis amongst women with CD4 counts >500 cells/cu mm [10].

In Ahdeich Grant et al. [11, 12], Hanskin's [13], Firnhasen [14], and Heard et al. studies [15, 16], they all said that low CD4 counts and increased HIV viral loads have an independent association with the incidence of delayed clearance of HPV infections as well as with the risk of progression of SIL (squamous intra-epithelial lesions).

In Sun et al. study, they found that the HIV-positive women were more likely to have persistent infection and depressed immune function, as measured by CD4 count, and were associated with greater persistence [17].

Effect of HAART on Colposcopic Findings and Correlation between PAP Smear, m HPV RNA and HAART

In the present study, pap testing was done in 75 cases out of which 4 were ASCUS and rest were negative for intra-epithelial lesion.

Out of 18 cases with minor colposcopic changes, 11 cases were on HAART for <1 year and rest of the 7 cases had received HAART for more than 1 year. One case with major colposcopic change not received HAART yet.

The present study, states that patients who had received HAART for longer durations develop good immunity and were less likely to acquire lower genital infections as compared to those who received HAART for lesser duration.

Also, in the present study, m HPV RNA oncotest was performed in 35 cases, only one came out to be positive, and all cases under study were on HAART.

From this, it can be said that HAART increases the clearance of oncogenic HPV type and likelihood of regressing the cervical SIL.

In the Canadian women's study, they followed 750 HIV-positive and 323 HIV-negative women during 1993–2002.

In this study total 467 pap smear were taken and in 456 cases HPV DNS analysis was done.

According to this study, HIV-positive women have increased prevalence (46.6 vs. 28.7 %), increased acquisition and decreased clearance of oncogenic HPV as compared to HIV-negative women.

Oncogenic HPV infection predicted progression of cervical dysplasia from normal to abnormal SIL.

Amongst HIV-positive women, HAART increased the likelihood of regression (from present to absent) of cervical SIL and increased clearance of oncogenic HPV types other than HPV 16 and HPV 18 [11].

In Paramsothy et al. study, they concluded that HAART is associated with a greater rate of regression of cytology determined cervical SIL (i.e. improved outcome of cervical disease with HAART) [18].

In Fife et al. study, a small decline in the proportions of subjects was demonstrated in whom at least 1 HPV type was detected, from 66 % at baseline to 49 % after 96 weeks of HAART initiation and a significant decrease in the proportion with high-risk HPV type from 62 % to 39 % [11].

In Heard et al. study, the prevalence of SIL decreased from 69 to 53 % and prevalence of colposcopic abnormalities decreased from 79 to 67 %.

Prevalence of Lower Genital Infections in HIV-Positive Women

In the present study, a total of 75 cases were studied in which 18 cases had minor colposcopic changes, i.e. lower genital tract infections.

Amongst them there were 5.5 % cases with candidiasis, 16.6 % cases with trichomoniasis, 1.3 % with HPV and 76.4 % with cervicitis due to other causes.

In Susan Cu-Uvin et al. [10] study, there were 3.1 % cases with candidiasis, 12.1 % cases with trichomoniasis, 64.3 % cases with HPV and 48.3 % cases due to other infections in HIV-positive women, whereas there were 1.9 % cases with candidiasis, 10 % cases with trichomoniasis, 27.6 % cases with HPV and 43.6 % cases due to other causes in HIV-negative women.

Conclusion

Thus from the present study, it can be said that prevalence of lower genital tract infections is more common in HIV-positive women [12], whereas it can very well be concluded that HIV-positive women who were on HAART showed an increased clearance of HPV infections because of increased immune function.

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Compliance with Ethical Standards

Conflict of interest Dr. Poorva Badkur, Dr. Kavita N. Singh and Dr. Vineeta Ghanghoriya declare that they have no conflict of interest and also the ethical statement is attached with the manuscript.

Informed Consent Consent was taken from all human subjects.

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