

Association between CD4+ T-cell count, atypical squamous cells and Schiller's test in women with HIV/AIDS

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ABSTRACT

Objective

Infection with HIV increased risk for the development of cancer, such as Kaposi's sarcoma and invasive cancer of the cervix. Given the importance of health promotion in women, the purpose of this study was to perform cytological screening (Pap smear) and identify any association between CD4+ T-cell, atypical squamous cells and the Schiller's Test in women with HIV/AIDS in Brazil.

Design

Descriptive and cross-sectional study.

Setting

Gynaecology outpatient clinic in Fortaleza, Ceará, Brazil.

Subjects

A total of 76 women with HIV/AIDS were examined and included in the study.

Main outcome measures

For data collection a questionnaire to gather sociodemographic, clinical, epidemiological and gynaecological data and the association between CD4+ T-cell count, atypical squamous cells and Schiller's test in women with HIV/AIDS were performed.

Results

Seventy-six women were evaluated, among which 43.5% had a positive Schiller's test and 94.8% manifested some type of inflammatory process. There was statistical significance between atypical squamous cells and the number of partners ($P=0.021$), age of first sexual intercourse ($P=0.003$) and positive Schiller's test ($P=0.008$). Of the patients with atypical squamous cells, eight had a low-grade, intraepithelial lesion, comprising the cytopathic effect of HPV and cervical intraepithelial neoplasia grade I (CIN I); three had intraepithelial lesion high-grade (CIN comprising II and III). There was a relationship between CD4+ T-cell counts and atypical squamous cells ($P=0.028$) and a positive Schiller's test ($P=0.030$).

Conclusion

Increased vulnerability occurred to cervix changes with a reduction in the CD4+ T-cell counts.

INTRODUCTION

Infection with the Human Immunodeficiency Virus (HIV) entails an increased risk for the development of cancer (Sasco et al 2010). Cancers such as Kaposi's sarcoma, non-Hodgkin lymphoma and invasive cancer of the cervix have been recognised for a long time as associated with HIV infection, and have been classified as AIDS-defining diseases (Tanon et al 2012).

The first report relating cervical intraepithelial neoplasia (CIN) to HIV was published by Bradbeer (1987). Other publications followed and, based on this information, showed that women infected with HIV had a high prevalence of HPV infection and CIN (Sun et al 1995; Feingold et al 1990).

In 1996, Brazil adopted a policy of free access to antiretroviral therapy (ART). With the increase in access to antiretroviral therapy, HIV-positive women are expected to live longer, potentially allowing sufficient time for cervical cancer to develop. Targeted screening could potentially alleviate the strain on resources needed to screen these women (Li et al 2012). Cervical cancer is a preventable cancer of the female genital tract. The disease is caused mainly by infection with persistent oncogenic human papilloma virus (HPV), which makes timely vaccination with HPV vaccine an effective primary prevention method. However, the cost of the vaccine makes it inaccessible in developing countries, thereby leaving secondary prevention through cervical cytology as the best alternative method of cervical cancer prevention (Dim 2012).

For women with HIV, the World Health Organization (WHO) recommends that the Pap smear should be offered at the initiation of monitoring, repeated in six months, and then annually, if normal. It should be repeated at more frequent intervals if: the preliminary investigation reports any change, if there was a prior history of HPV infection, after treatment of lesions, and with a diagnosed advanced stage of immunodeficiency, with CD4+ T-cell counts < 200 cells/mm³. In case of detection of atypia, women should be referred for colposcopy (WHO 2006). As described in this study, this procedure is also adopted in the health services that cater to women with HIV/AIDS in Brazil.

HIV/AIDS is one of the most serious public health problems worldwide, representing a challenge in many ways, especially due to the absence of an effective treatment that leads to a cure, in addition to the social and economic barriers that interfere with adherence to the treatment regimen. Considering the importance of health promotion in women, the aim of this study was to perform cytological screening (Pap smear) and identify any association between CD4+ T-cell, atypical squamous cells and Schiller's Test in Women with HIV/AIDS, treated at reference service for cervical cancer in Fortaleza, Ceará, Brazil.

METHOD

This was a cross-sectional study conducted at the Institute for Cancer Prevention, in Fortaleza, Ceará, Brazil. This is a reference centre in the State of Ceará, for prevention of gynaecological cancer that offers outpatient and hospital care, specialising in gynaecology and the prevention and treatment of cancer. A convenience sample was used, with the following inclusion criteria women with HIV/AIDS, receiving treatment in 2008, and 18 years of age or older. The only exclusion criterion was history of hysterectomy.

The women completed a nursing consultation and a questionnaire was administered to obtain sociodemographic, clinical, epidemiological and gynaecological data. Following data collection, a gynaecological examination was performed, which included a Pap test. The analysis of the collected material was performed at the institution through its accredited laboratory.

To perform the statistical procedures, the Statistical Package for the Social Sciences (SPSS® for Windows®) version 19.0 was used. To estimate the association between dichotomous variables, comparing proportions,

the chi-square or Fisher's exact test was applied. For the comparison between averages the Student's t-test was used, when the distribution of the independent variable approached a normal distribution. In the applied tests the significance level of 5% was adopted.

The study followed all regulatory instructions regarding research involving human subjects, and the project was approved by the Research Ethics Committee of the São José Hospital of Infectious Diseases, under Protocol No 022/2007. All participants received information about the study and signed an informed consent form.

RESULTS

The mean age of the 76 women who participated in the study was 37.4 years. Most came from the city of Fortaleza and had up to eight years of school. It was observed that 73.7% of women earned between one and four times the minimal salary, and 48.7% had informal employment. Regarding religion, most were catholic (table 1).

Of the total participants, 90.8% reported a heterosexual exposure category and 76.3% had developed AIDS. For the CD4+ T-cell counts, 40.8% of the women had levels below 350 cells/mm³, and only 76.3% were using antiretroviral drugs. Most outpatients had monitoring on a quarterly basis. Regarding the data obtained from the gynaecological exam, external inspection found that 18.4% of women had condylomatous lesions. The Schiller's test was positive in 43.5% of women. Regarding the Pap test, 94.8% of the women had some type of inflammation, ranging from mild to severe. Of the patients with atypical squamous cells, eight had a low-grade, intraepithelial lesion, comprising the cytopathic effect of HPV and cervical intraepithelial neoplasia grade I (CIN I); three had intraepithelial lesion high-grade (CIN comprising II and III) (table 2).

Table 1: Sociodemographic characteristics of women with HIV/AIDS having cervical cancer screening

Variables	N	%
Age (in years) *		
≤ 29	15	19.7
30-39	32	42.1
≥ 40	29	38.2
Residence		
Fortaleza	66	86.8
Rural areas	10	13.2
Years of Study		
Illiterate	06	7.9
≤ 8 years	44	57.9
> 8 years	26	34.2
Family Income (minimum salary) **		
No income	03	4.0
< 1	08	10.5
1 - 4	56	73.7
5 - 8	09	11.8
Occupational Situation		
Working/Informal job	37	48.7
Unemployed	33	43.4
Retired/Pensioner	06	7.9
Religion		
Catholic	51	67.1
Non-Catholic	21	27.6
None	04	5.3

*Mean age: 37.4 years old; Standard deviation: 8.8.

**Minimum salary at that time: R\$ 465.00 (USD \$209).

Table 2: Epidemiological, clinical and gynaecological characteristics of women with HIV/AIDS having cervical cancer screening

Variables	N	%
Phase of the illness		
HIV	21	23.7
AIDS	55	76.3
Exposition category		
Heterosexual	69	90.8
Bisexual	01	1.4
Transfusion	03	3.9
Without answer	03	3.9
Antiretroviral therapy		
Yes	58	76.3
No	18	23.7
CD4+ T-cell count (mm³)*		
< 200	16	21.1
200-350	15	19.7
351-500	18	23.7
> 500	27	35.5
Time of the evaluations		
Monthly	11	14.5
Quarterly	54	71.0
Semi-annual	11	14.5
Condylomatous lesions		
Yes	14	18.4
No	62	81.6
Iodine test		
Negative	33	43.5
Positive	43	56.5
Schiller's test		
Negative	43	56.5
Positive	33	43.5
Descriptive diagnostic		
Normal	01	1.3
Inflammation	72	94.8
Immature metaplasia	01	1.3
Atrophy with inflammation	02	2.6
Atypical squamous cells		
None	58	76.3
Cells possibly non neoplastic	06	7.9
With indefinite origin	01	1.3
HPV and CIN I	08	10.5
NIC I and CIN II	03	4.0

*CD4+ T-cell count (mm³): Mean: 454.13;

Standard deviation: 249.36.

Most women had a regular partner at the time of the study (67.1%), and indicated their use of condoms (73.6%). Regarding the development of sexually transmitted diseases, 46.0% of the women reported having already had some disease, with HPV infection being cited by 51.7% of women.

The researchers conducted an association between the clinical, epidemiological, gynaecological variables, and the presence of atypical squamous cells. A statistically significant association between the presence of atypical squamous cells and the number of sexual partners ($P=0.021$), age at first intercourse ($P=0.003$), negative iodine test ($P=0.008$) and positive Schiller's test ($P=0.008$) was identified (table 3).

Regarding access to the screening exam, 85.5% of women found it difficult to schedule and obtain the preventive screening. Likewise, when inquiring about advance directives on the preventative health services exam, 46.1% reported not having been advised by a health professional or organisation about the need for the examination for preventing cervical cancer.

Table 4 shows the association between the variable CD4+ T-cell count, presence of atypical squamous cells and the Schiller's test result in women infected with HIV. There was a statistically significant association between the CD4+ T-cell count and atypical squamous cells ($P=0.028$), as well as the presence of a positive Schiller's test and CD4+ T-cell counts ($P=0.030$). This finding demonstrated an increased vulnerability to cervix changes with a reduction in the CD4+ T-cell counts.

DISCUSSION

AIDS is one of the biggest health problems today, based on its pandemic character and its severity. HIV infection has emerged as a chronic illness that is often controllable with ART. However, high levels of adherence remain necessary to achieve optimal clinical benefits of ART, and to avoid developing drug-resistant strains of HIV (Kalichman et al 2013; Cunha and Galvão 2010).

The study showed that some women had abnormal gynaecological findings, through use of the Schiller's test and Pap smear. Of these, 10.5% had CIN I and HPV, and 4.0% had CIN I and CIN II. These findings were consistent with other research on the subject,

that has indicated these changes were common in women with HIV/AIDS, and that squamous intraepithelial lesions of the cervix were more frequent in HIV-positive women overall (Atashili et al 2012; Parham et al 2006).

The findings in this study regarding the positive Schiller's test and presence of atypia corroborate the data mentioned in the current literature. Therefore, the results showed the need to enact strategies for the prevention of cervical cancer in women infected with HIV, since the surveillance of gynaecologic changes allows early detection and eradication of HPV infection and CIN, minimising the incidence of cervical cancer. It is believed that health services need to establish an urgent priority for assistance in preventing cancer of the cervix in HIV-infected women, that they can define and track cases with detected changes, in order to encourage prevention and control of cancer in these women (WHO, 2006).

By associating the presence of atypical squamous cells with other variables, we found statistical significance in relation to the number of sexual partners, age at first intercourse and a positive Schiller's test. In this context, the study showed that the multiplicity of sexual partners during a woman's lifetime was a major risk factor for HPV infection and other genital changes. Women with such practices are more vulnerable and can more easily become infected with sexually transmitted diseases, including HIV, a fact that may favour the development of cervical cancer (Jha et al 2012, Banura et al 2011).

Table 3: Association between clinical, epidemiological and gynaecological variables and atypical squamous cells

Variables	Atypical squamous cells		
	Yes N (%)	No N (%)	P Value
Number of partners			
1 - 4	2 (5.1)	37 (94.9)	0.021**
> 4	9 (24.3)	28 (75.7)	
In the last year			
None	2 (10.5)	17 (89.5)	0.720
1 or more	9 (15.8)	48 (84.2)	
Stable partner			
Yes	8 (15.7)	43 (84.3)	1.000
No	3 (12.0)	22 (88.0)	
Live with the partner			
Yes	6 (13.0)	40 (87.0)	0.430
No	5 (16.6)	25 (83.4)	
Time of the relationship (in years)			
≤ 5	3 (12.5)	21 (87.5)	1.000
> 5	8 (15.3)	44 (84.7)	
Use of condoms			
Yes	9 (16.0)	47 (84.0)	1.000
No	2 (10.0)	18 (90.0)	
Time of the last diagnosis of colon cancer			
≤ 1 year	5 (14.2)	30 (85.8)	1.000
2 or more years	6 (14.6)	35 (85.4)	
Presence of cancer in the family			
Yes	4 (11.1)	32 (88.9)	0.527
No	7 (17.5)	33 (82.5)	
Age of the first relative (in years)			
≤ 19	10 (27.0)	28 (73.0)	0.003**
> 19	1 (2.6)	37 (97.4)	
History of STD			
Yes	7 (20.0)	28 (80.0)	0.167
No	3 (7.5)	37 (92.5)	
Condylomatous lesions			
Yes	3 (21.4)	11 (78.6)	0.415
No	8 (12.9)	54 (87.1)	
Iodine test			
Negative	9 (27.3)	24 (72.7)	0.008**
Positive	2 (4.7)	41 (95.3)	
Schiller's test			
Negative	2 (4.7)	41 (95.3)	0.008**
Positive	9 (27.3)	24 (72.7)	

*Fisher's exact test. **P<0.05.

Table 4: Association between CD4+ T-cell counts, atypical squamous cells and the Schiller's test

	CD4+ T-cell counts			P Value*
	< 200 mm³	200-500 mm³	> 500 mm³	
Atypical squamous cells				
Yes	4 (30.0)	6 (18.2)	1 (3.70)	0.028
No	12 (70.0)	27 (81.8)	26 (96.3)	
Schiller's test				
Positive	7 (70.0)	18 (54.5)	8 (33.3)	0.030
Negative	9 (30.0)	15 (45.5)	19 (66.7)	

*Test for linear trend.

An independent risk factor for the development of CIN was having more than five sexual partners, even when the woman was not a carrier of HPV. Furthermore, if the number of lifetime sexual partners was less than or equal to five, the chances of CIN grade II or III recurrence was 60% (Mbizvo et al 2005; Pudney et al 2005). Other studies with HIV-infected women corroborated the vulnerability of women in relation to multiple partners for the acquisition of cervical cancer (Jha et al 2012, Banura et al 2011).

In relation to early onset of sexual activity, when this occurred before age 16, there was a greater chance of HPV infection, which, consequently, increased the risk for the development of CIN and cervical cancer. This was due to the fact that the uterine transformation zone of these women was in the early process of metaplasia, so intraepithelial neoplastic lesions could progress more rapidly because of the immaturity of the cervix (Pudney et al 2005).

In this study the positive Schiller's test was associated with the presence of atypical squamous cells, showing the relationship between cellular changes and clinical alteration identified by the material collected in the screening. Preventing cervical cancer requires specialised nursing intervention. There is need for nurses to be able to collect the Pap smear and to develop guidelines aimed at promoting health to assist in maintaining the quality of life of women with HIV/AIDS. Moreover, the practice of nursing in its technical dimension provides comfort for the patient who is emotionally fragile, soothing her anxieties and fears, from the caregiver's approach during the execution of her practice.

Globally, many women with HIV are of reproductive age and many acquire the virus through sexual contact. There is also an increased risk for other sexually transmitted diseases, a fact which facilitates contamination and the development of cervical cancer. Therefore, early initiation of sexual activity, associated with consistently unprotected sex, amplifies the risk of acquiring sexually transmitted diseases, including HIV infection, and therefore the greater likelihood of developing cervical cancer in HIV-positive women (Stuardo et al 2012; Williams et al 2011). Following an active surveillance protocol that ensures gynaecologic diagnosis and treatment of gynaecological problems in women with HIV is necessary. This is especially true because the reduction in mortality from cervical cancer is possible through health promotion and the early detection of cases of precursor lesions by means of structured screening (WHO, 2006).

When evaluating immune function, it was observed that the CD4+ T-cell counts were statistically significant among patients with a positive Schiller's test ($P=0.030$) and the presence of atypical squamous cells ($P=0.028$). Immune status is one of the cofactors of paramount importance, since in immunocompromised patients, carcinogenesis-induced genital HPV is established suddenly in the presence of immunosuppression, so that women with HIV are more likely to develop cervical intraepithelial neoplasia, demonstrating an association between the severity of the neoplasia and immunosuppression (Harris et al 2005).

Currently, the presence of clinical signs of immunodeficiency, such as the CD4+ T-cell counts and quantification of viral load, are the main parameters used to initiate and monitor antiretroviral therapy in patients with AIDS. Since the early years of the epidemic, monitoring of CD4+ T-cell counts has been used as a predictive laboratory parameter of HIV disease prognosis, and also as an excellent indicator of the magnitude of risk for major opportunistic infections, such as cervical cancer, especially in patients with symptomatic disease (Heikinheimo and Lähteenmäki, 2009).

Studies indicated that patients with CD4+ T-cell counts less than 200 cells/mm³ had high-risk oncogenic HPV more frequently, so that the risk for developing intracervical cancer was higher in this group, or as immunosuppression increased, there was a greater vulnerability of developing cervical cancer (Tanon et al 2012; WHO 2006). Given this, it becomes clear that healthcare professionals should monitor the evaluation of immunosuppression of HIV-infected women due to possible changes of the cervix.

CONCLUSION

In conclusion, depending on the findings, there is a need to encourage HIV-infected women to undertake the preventive cervical cancer screening, and it becomes necessary to use appropriate information so that they are able to perform self-care. The importance of encouraging disease prevention and health promotion in relation to early diagnosis is verified by the fact that when the cancer is diagnosed in its early stage and treated appropriately, the prognosis for cure is much higher. Health promotion demands the coordinated action of those involved; it is essential to accountability, active management participation, specialised services and health professionals for mediating this practice. Associated with this, there is an urgent need for specialised services to reorganise its actions for disease prevention among women, in particular, for the prevention of cervical cancer.

Women living with HIV/AIDS are vulnerable to cervical cancer, and preventive actions are required to provide specific information associated with the early detection of disease, increasing the level of knowledge, encouraging self-care, and improving the quality of healthcare services that meet the needs of this clientele.

A limitation of this study was that the sample only contained 76 women living with HIV/AIDS, which is due to the low level of knowledge of women about the importance of having the pelvic exam, as well as socioeconomic issues that prevent access to the examination.

This study demonstrated the need to implement a specific service for prevention of cervical cancer using the screening protocol for HIV-infected women. It is suggested, however, that there is a need for training of nurses specialists in this area, because this work transcends the technical dimension; it also involves the establishment of a therapeutic relationship based on competence, confidence and commitment to the female population with HIV/AIDS. Thus, cervical cancer prevention should be performed efficiently, so that the vulnerabilities described in this study can be minimised.

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