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Cervical Cytology and Histopathologic Abnormalities in Women living with AIDS in São Paulo, Brazil

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Abstract

Background: Women living with HIV/AIDS present with a higher prevalence of human papillomavirus (HPV) infection, higher rates of squamous intraepithelial lesions, and are more susceptible to invasive cervical carcinoma progression.

Objective: We assessed the frequency of precursory cervical lesions of cancer and its risk factors for women living with HIV/AIDS.

Methods: Sociodemographic, clinical, behavioral, and laboratory data were collected from medical records from 2008 to 2009 and analyzed using forward stepwise logistic regression.

Results: Medical records of 631 women were reviewed; mean age at AIDS diagnosis was 34 years old (interquartile range = 29–40 years old), 32% were <16 years old at first sexual intercourse; 61% had 5 sexual partners during life; 43% had been living with AIDS for 9 years; 47% reported previous sexually transmitted infections; 44% presented with HPV infection; and 10% presented with high squamous intraepithelial lesions. Presenting high squamous intraepithelial lesions was significantly associated with home district Human Development Index, age at AIDS diagnosis (>40 years old), time of AIDS diagnosis (>8 years), CD4⁺ cell count <350/mm³, and HPV infection.

Conclusions: Frequent squamous intraepithelial neoplasia in these women shows the importance of gynecologic examinations in routine care and follow-up required by those who present with cervical lesions.

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Keywords

AIDS; cervical cancer; HIV; HPV; high-grade lesion

INTRODUCTION

Women who live with HIV/AIDS present significantly high rates of squamous intraepithelial lesions (SIL) and are more susceptible to invasive cervical carcinoma progression than HIV-negative women.^{1,2} The prevalence of human papillomavirus infection (HPV) is usually greater among HIV-infected women^{3,4} than among HIV-uninfected women; this may be explained by the persistence of HIV viral load, which increases the risk of developing SIL.^{5,6}

There is no HIV infection surveillance in Brazil, thus only AIDS is a reportable disease. The AIDS prevalence rate in the country is 0.6%; 0.8% among men and 0.4% among women with a significant impact on reproductive health. From 1980 to June 2009, 544,846 cases of AIDS were reported in Brazil and among these 201,333 cases (36,9%) were reported in Sao Paulo state.⁷ The male to female ratio in Brazil has decreased from 26.7 in 1985 to 1.5 in 2009.⁷

The combination of a systematic antiretroviral therapy (ART) program since 1996, strong efforts to prevent opportunistic infections, and the referral of HIV-infected patients for specialized care has resulted in longer survival among people living with AIDS in Brazil. Long-term survival has led to increased efforts to diagnose and treat chronic diseases including precursory diseases of cervical cancer that may threaten the quality of life and survival of women living with AIDS.⁸ The importance of SIL is reflected by the inclusion of cervical cancer as an AIDS-defining illness in 1993 by the Centers for Diseases Control and Prevention⁹ in the United States.

The goals of this study were to describe the frequency of cervical cancer precursor lesions and risk factors for these lesions in women living with AIDS in Brazil.

METHODS

This is a cross-sectional study carried out in the Reference and Training Center for Sexually Transmitted Diseases and AIDS in the city of Sao Paulo, Brazil. This center has about 1800 women in follow-up for HIV/AIDS. Data were collected from medical records of women living with AIDS, under ART. Women scheduled for a gynecological appointment in the outpatient gynecological clinics of reference center for sexually transmitted disease (STD)/AIDS between July 1, 2008 and May 31, 2009 were included in the study. Women living with AIDS but not receiving ART were excluded from the study as were those with no CD4⁺ results or those with no gynecological consultation described in medical records.

Independent variables were grouped as sociodemo-graphic, behavioral, or clinical. Sociodemographic variables included age at AIDS diagnosis, education, race, and Human Development Index (HDI) of home district. HDI is a composite statistic used to rank

countries by level of “human development.”. The statistic is composed from data on life expectancy, education, and per capita rate. Education and HDI were used as indicators for socioeconomic level. Data were collected from medical records and linked to the HDI database of the city of Sao Paulo. Behavioral variables included age at first sexual intercourse and number of lifetime sexual partners. Clinical variables included previous sexually transmitted infection (STI) (Chlamydia, Gonorrhea, Trichomonas, hepatitis B and C virus, syphilis, HPV, herpes simplex virus 2), time since AIDS diagnosis, and CD4⁺ cell count.

Papanicolaou smear of endocervix and ectocervix for cervical cytology were classified according to the Bethesda classification for changes characteristic of HPV infection. HPV cytological changes were diagnosed by the presence of koilocytotic atypia and SIL of the cervix. The outcome of interest was the presence of high SIL, including carcinoma or previous cervical conization surgery.

A bivariate analysis was conducted to investigate associations between dependent and independent variables and as a strategy to select variables to adjust for the logistic regression model. χ^2 test was used for comparing proportions and Student *t* test for comparing means. Odds ratios were calculated for each independent variable. Forward stepwise logistic regression was conducted to develop a final model. STATA SE 10.1 (STATA CORP STATA Statistical Software: release 10.1; Stata Corporation, College Station, TX) was used for data analysis.

Ethical and Research Committee of Reference and Training Center of STD/AIDS of the city of Sao Paulo, Brazil, approved this project.

RESULTS

There were 710 women with clinic visits during the study period, though 79 (11%) of them were excluded for the following reasons: 29 had no early gynecologic follow-up, 23 did not receive ART, 18 were HIV negative, and 9 had HIV infection acquired by vertical transmission and did not report sexual activity.

Among 631 women included in our analysis, 64 were diagnosed with high SIL, a prevalence of 10.1% [95% confidence interval (CI): 7.7% to 12.5%]. Socioeconomic characteristics are presented in Table 1. Patients with high SIL were more likely to be older than 40 years old (52% vs. 25%, $P < 0.001$) and have a lower HDI (88% vs. 25%, $P < 0.001$) than those who did not present with high SIL.

Table 2 presents behavioral and clinical characteristics of women living with AIDS with and without high SIL. More than half of these women (57%) started their sexual life at 16 years of age or above, and 61% had 5 sexual partners during their lives. Women with high SIL had AIDS diagnosis for more than 9 years (76% vs. 39%, $P < 0.001$) and present CD4⁺ count, 350 cell/mm³ (83% vs. 37%, $P < 0.001$) more frequently than those women without high SIL. Previous STI were reported by 47% of women; 44% reported HPV, 20% reported herpes simplex virus 2, and 18% had a history of 2 STI.

The last Pap smear test was done within 1 year in 80% of cases, 13% from 1 to 3 years, and 7% >3 years. The time interval between last two Pap tests was <1 year in 36%, 1–3 years in 46%, and >3 years in 10%. The last Pap smear results were normal for 90%, 9% low-grade lesions and 2% high-grade lesions. Colposcopy was performed in 35% of cases.

Associated risk factors for high SIL in multivariate analysis were HPV cytological changes [odds ratio (OR)_{aj} = 68.6 (95% CI: 11.6 to 404.6)], CD4+ T-lymphocyte cells counting, 350 cells/mm³ [OR_{aj} = 24.5 (95% CI: 2.7 to 224.9)], HDI of home district <0.50 [OR_{aj} = 3.3 (95% CI: 1.1 to 10.8)], time since AIDS diagnosis >8 years [OR_{aj} = 2.9 (95% CI: 1.3 to 6.5)], age at AIDS diagnosis (>40 years old) [OR_{aj} = 2.7 (95% CI: 1.2 to 6.0)] (Table 3).

DISCUSSION

We found a prevalence rate of 10.1% for high SIL among women living with AIDS attending a reference center for HIV/AIDS in Brazil. High SIL was frequent in this population, and it shows the importance of routine monitoring for these women through Pap smear tests and follow-up of those with cervical abnormalities. Other studies also described SIL as frequent lesions in HIV-infected women.^{1,10–12}

A low human development index increases risk of high SIL. Indicators such as low personal/household income, unemployment, lack of health insurance, and low HDI may all be associated with decreased accessibility to health services and low adherence to antiretroviral treatment,¹³ despite free access and distribution of ART in Brazil. Kalichman et al¹⁴ reported educational level as a marker for social inclusion and for patient relationship with health services in Brazil.

HPV is one of the most important risk factors for cervical cancer.^{15,16} In our study, HPV cytological changes were frequent (44%) and were associated with high SIL. HPV infection and SIL are common in this population.^{1,3,12} Women living with HIV may be asymptomatic; however, women with fast progressing SIL must be tested for HIV as SIL may be a sign of immunosuppression. On the 70's, a hypothesis that HPV infection was involved in cervical carcinogenesis was suggested,^{17,18} and subsequent studies showed that nearly all cervical neoplasias occur in HPV-positive patients and only specific types of virus are associated with invasive carcinoma.³

Other clinical variables associated with high SIL in this study were CD4⁺ cell counts, 350 cells/mm³. Other studies have suggested that the frequency of HPV persistence varies inversely with CD4⁺ count and that higher HPV prevalence and incidence of oncogenic HPV types are found in HIV-infected patients, especially those with lower CD4⁺ counts.^{11,19,20} These data suggest that the level of CD4⁺ is important in the pathogenesis of HPV infection in HIV patients.

Being older than 40 years at AIDS diagnosis and living with AIDS for more than 8 years were associated with high SIL. These findings can be explained by the fact that women older than 45 years have higher risk of developing cancer and, individuals who survive several years after an AIDS diagnosis have persistent excess risk for both AIDS-defining and non-AIDS-related malignancies.²¹

The present study had some limitations. First, we used secondary data. Furthermore, the results cannot be extrapolated to other populations of women living with AIDS because we used a convenient sample in one reference center for STD/AIDS in Brazil that only included women who sought care. Moreover, we cannot establish that the risk factors associated with high SIL were causally related because of the retrospective design of the study. The possibility of response bias also cannot be discarded due to the tendency of individuals to give socially acceptable self-reported responses during medical appointments. Also, lack of accuracy in the women's responses with respect to age at first sexual intercourse, number of sexual partners, and drug use, among others, cannot be excluded. The study population was composed entirely of women living with AIDS receiving care and ART within the Brazilian National Health Service, thus excluding all consultations in the private sector. Despite these limitations, data registered in the medical records was satisfactory and it showed that secondary data could be used to monitor the implementation of STI prevention and cervical cancer programs. Nevertheless, the high quality of data from the primary public outpatient clinic in the city attending AIDS patients strengthens the study.

Performing routinely cervical cytological examinations is recommended and any degree of abnormality in this test should be referred to colposcopy assessment.²² HIV-positive women with cervical invasive carcinoma normally present faster evolution and greater risk of disease recurrence.¹ Cervical cancer incidence in HIV-positive women is not changed with use of ARV therapy.²³ Therapeutic management is the same for any woman, independently of her HIV serology, but with poorer prognosis in women with AIDS.^{1,12}

Despite Pap smear test availability for universal screening for cervical cancer in Brazil, the prevalence and incidence rates of this disease did not decrease consistently, characterizing a significant public health problem.^{24,25} In addition, regardless of the fact that the Pap smear is a low-cost test and easily available for women with AIDS in Brazil, there is a need to identify innovative interventions that reduce social, cultural, and environmental influences on HPV infection and cervical cancer in this population.

Screening, treatment, and prevention counseling and support in health facilities should be considered and evaluated as a core component of cervical cancer prevention efforts in gynecological outpatients clinics for HIV patients. Our results reinforce the importance to perform routine gynecologic examinations for women with CD4⁺ cells count <350 cells/mm³.

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TABLE 1.
Sociodemographic Characteristics of Women living with AIDS—São Paulo, Brazil, from 2008 to 2009

High-grade lesions							
Characteristics	Yes (n = 64)		No (n = 567)		Total (n = 631)		P
	n	%	n	%	n	%	
Age (at AIDS diagnosis)							
Up to 40 years old	31	48.4	428	75.5	459	72.7	<0.001
>40 years old	33	51.6	139	24.5	172	27.3	
	64	100.0	567	100.0	631	100.0	
Years of education (years)							
None	1	1.6	6	1.1	7	1.1	0.712
1–4	5	7.8	45	7.9	50	7.9	
5–8	27	42.2	226	39.9	253	40.1	
9–11	26	40.6	210	37.0	236	37.4	
12 or more	4	6.3	75	13.2	79	12.5	
Unknown	1	1.6	5	0.9	6	1.0	
Race (self-referred)							
White	33	51.6	360	63.5	393	62.3	0.005
Black	27	42.2	199	35.1	226	35.8	
Others	4	6.3	5	0.9	9	1.4	
Unknown	0	0.0	3	0.5	3	0.5	
HDI of home district							
>0.500	8	12.5	423	74.6	431	68.3	<0.001
0–0.500	56	87.5	144	25.4	200	31.7	

TABLE 2.
Behavior and Clinical Characteristics of women living with AIDS — São Paulo, Brazil, from 2008 to 2009

Characteristics	High-grade lesions						Total (n = 631)		P
	Yes (n = 64)			No (n = 567)			n	%	
Age at first sexual intercourse									0.074
Up to 16 years old	27	42.2	180	31.7	207	32.8			
More than 16 years old	28	43.8	332	58.6	360	57.1			
Unknown	9	14.1	55	9.7	64	10.1			
Lifetime number of sexual partners									0.058
1–2	8	12.5	133	23.5	141	22.3			
3–5	24	37.5	218	38.4	242	38.4			
6 and more	20	31.3	107	18.9	127	20.1			
Unknown	12	18.8	109	19.2	121	19.2			
STI									<0.001
No	1	1.6	301	53.1	302	47.9			
Yes	63	98.4	233	41.1	296	46.9			
Unknown	—	—	33	5.8	33	5.2			
	64	100.0	567	100.0	631	100.0			
HPV cytological changes									<0.001
No	2	3.1	351	61.9	353	55.9			
Yes	62	96.9	216	38.1	278	44.1			
	64	100.0	567	100.0	631	100.0			
HSV									0.969
No	51	79.7	453	79.9	504	79.9			
Yes	13	20.3	114	20.1	127	20.1			
Time of AIDS diagnosis									<0.001
18 years	16	25.0	345	60.8	361	57.2			
9 years or more	48	75.0	222	39.2	270	42.8			
CD4 ⁺ cell counting (cell/mm ³)									<0.001
>500	1	1.6	126	22.2	127	20.1			

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Characteristics	High-grade lesions				Total (n = 631)		P
	Yes (n = 64)		No (n = 567)		n	%	
	n	%	n	%	n	%	
350–500	10	15.6	234	41.3	244	38.7	
<350	53	82.8	207	36.5	260	41.2	

TABLE 3.

Bivariate and Multivariate Analysis of Associated Factor for High-Grade Lesion of Women Living With AIDS—Sao Paulo, Brazil, 2008–2009

Users characteristics	Bivariate analysis			Multivariate analysis		
	OR	95% CI	P	OR _{adj}	95% CI	P
HPV cytological changes						
No	1	—	—	1	—	—
Yes	50.4	12.2–208.0	<0.001	68.6	11.6–404.6	<0.001
CD4 ⁺ cell counting (cell/mm ³)						
>500	1	—	—	1	—	—
350–500	5.4	0.7–42.5	0.11	0.74	0.1–7.3	0.799
<350	32.3	4.4–236.2	0.001	24.5	2.7–224.9	0.005
HDI of home district						
>0.500	1	—	—	1	—	—
0–0.500	20.6	9.6–14.2	<0.001	3.3	1.1–10.8	0.047
Time of HIV diagnosis (years)						
1–8	1	—	—	1	—	—
>8	4.7	2.6–8.4	<0.001	2.9	1.3–6.5	0.012
Age level (for AIDS diagnosis)						
Up to 40 years old	1	—	—	1	—	—
>40 years old	3.3	1.9–5.5	<0.001	2.7	1.2–6.0	0.019
No. of lifetime Sexual partners						
1–2	1	—	—	—	—	—
3–5	1.8	0.80–1.19	0.153	—	—	—
6 and more	3.1	1.32–7.33	0.010	—	—	—
STI						
No	1	—	—	—	—	—
Yes	48.8	6.71–354.2	<0.001	—	—	—
Race (self-referred)						
White	1	—	—	—	—	—
Black	1.5	0.86–2.53	0.153	—	—	—
Others	8.7	2.23–34.1	0.002	—	—	—

OR, odds ratio (nonadjusted); OR_{aj}, odds ratio adjusted.

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