Prevalence of Anogenital Warts in Men with HIV/AIDS and Associated Factors

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Abstract: *Background*: Infection with human papilloma virus (HPV) is the most common sexually transmitted disease in the world. Among the 630 million new cases of HPV that occur each year, 30 million develop anogenital warts. Although subclinical infection with HPV is the most common cause, genital warts are also associated with immunosuppression caused by HIV. In view of the high prevalence of HPV/HIV co-infection particularly among men who have sex with men, the objectives of this study were to determine the prevalence of anogenital warts in men with HIV/AIDS and to identify associated factors.

Methods: A cross-sectional study was conducted on 159 men with HIV/AIDS consecutively selected at a referral service in Botucatu, São Paulo, Brazil, in which the association between sociodemographic, behavioral and clinical variables and the presence of anogenital warts was evaluated. After hierarchical analysis of the data, variables presenting a p value ≤ 0.2 were entered into an unconditional multivariate logistic regression model.

Results: Forty-nine (31%) of the HIV-positive patients had anogenital warts. The mean age was 44.6 ± 9.6 years. The main factors associated with the presence of anogenital warts were irregular antiretroviral treatment and genital herpes(HSV).

Conclusion: The present study demonstrate that anogenital warts occur in almost one-third of the male population infected with HIV and factors associated with a higher risk of being diagnosed with anogenital warts were irregular cART use and co-infection with HSV, other variables could not be associated.

Keywords: AIDS, Anogenital warts, CD4+ T lymphocytes, HPV, men.

INTRODUCTION

According to World Health Organization (WHO) estimates, 35.3 million people in the world were infected with the human immunodeficiency virus (HIV) in 2012[1]. Of these, 39% were men older than 15 years [2]. In Brazil, approximately 608,000 cases of AIDS have been notified between the identification of the first case in 1980 and June 2011, 56% of them in the southeastern part of the country.

Human Papillomavirus

Human papillomavirus (HPV) is a highly species-specific and strictly epitheliotropic double-stranded DNA adenovirus, which preferentially infects cutaneous or mucocutaneous tissue, affecting stratified squamous cells [3]. HPV can cause benign lesions such as condyloma acuminata, or malignant lesions that are frequently subclinical, a fact making diagnosis difficult and increasing the risk of progression to cancer [4].

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In the United States, the prevalence of anogenital infection with HPV is 15% in the general population [5]. A Brazilian study showed a prevalence of anal infection of up to 12% in the male heterosexual population [6]. The Brazilian Ministry of Health registers 137,000 new cases of HPV every year and experts believe that the smaller number of men diagnosed with this infection is due to fact that men rarely seek urology services because of prejudice or lack of information, among other reasons [4].

Co-Infection with HIV and HPV

It is well established that the number of Langerhans cells [7], CD4+ T lymphocytes, macrophages, neutrophils and natural killer cells [8] is reduced in patients infected with HIV, a fact leading to changes in local immunity and modulating HPV infection at the tissue level. Chaturvedi *et al*. [9] demonstrated a high incidence of HPV-associated cancer in patients with low T-cell counts and that the frequency and magnitude of HPV detection increase with increasing immunosuppression. There are few circulating HPV-specific memory cells involved in the immune response to infection with this virus and the proportion of these cells decreases even further because of the intense

depletion of this cell population mediated by HIV. In addition, the specific immune response may not be restored completely after recovery of the immune system, a fact that would explain the limited benefits of combination antiretroviral therapy (cART) for the regression of HPV lesions [10].

The objectives of the present study were to determine the prevalence of anogenital warts in men infected with HIV, to evaluate the association between these lesions and CD4+ T lymphocyte count and plasma HIV load, and to identify factors associated with HPV infection.

MATERIAL AND METHODS

The presence of anogenital warts was investigated in a descriptive cross-sectional study involving 159 men with HIV/AIDS. Male patients older than 18 years diagnosed with HIV, who had already initiated sexual activity, had the mental and physical capacity to participate in the inspection of anogenital skin and to respond to an interview, and had agreed to participate in the study by signing the free informed consent form, were included. The patients were selected consecutively and submitted to physical examination and an interview of 10 to 15 min for the collection of sociodemographic, behavioral and clinical data. The questionnaire was developed specifically for this study and had been tested previously in the first 50 patients. The subjects were recruited between May and December 2011 from the Domingos Alves Meira Specialized Outpatient Service of Infectious Diseases at the Botucatu Medical School (FMB), UNESP, Botucatu, São Paulo, Brazil.

The clinical diagnosis of anogenital lesions was made by physical examination. For this purpose, gauze soaked in 5% acetic acid was applied to the anogenital skin surface for about 2 min for visualization of acetowhite lesions suggestive of infection with HPV. The diagnosis of lesions suggestive of condyloma acuminata was confirmed clinically by a specialist.

Flow cytometry was used for CD4+ T lymphocyte count and the results are expressed as the absolute number of cells per mm3. Plasma HIV load was determined by the branched

DNA assay and the results are reported as the absolute number of RNA copies of the virus per milliliter plasma. These tests were conducted at the Blood Center of FMB during routine care of the HIV/AIDS patients. The results of tests performed at the time of diagnosis of HIV infection and up to 3 months before or after inclusion in the study were considered for analysis.

The antiretroviral drugs used were divided into the six classes available: nucleoside and non-nucleoside analog reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, fusion inhibitors, and CCR5 co-receptor antagonists.

Statistical Analysis

First, bivariate analysis was performed to evaluate primary associations between the variables in each group. Categorical variables are expressed as relative frequency and were compared by the chi-squared test or by the chi-squared test for trend for variables lying on an ordinal scale. Continuous and discrete quantitative variables are reported as the mean or median and were analyzed by the Student *t*-test or Mann-Whitney test if the distribution was nonparametric. The Shapiro-Wilk test was used to determine whether the variables showed a normal distribution.

Next, independent variables were selected from an unconditional multiple logistic regression model with a hierarchical structure to control for confounding factors (Table **1**). The variables were entered progressively into the model according to each hierarchical level as long as they presented a p value ≤ 0.2 [11].

Associations were evaluated using odds ratios and their 95% confidence interval, with a p value < 0.05 indicating significance. CD4+ T lymphocyte count and HIV load are expressed as the median and interquartile range. The SPSS 17.0 software was used for statistical analysis.

RESULTS

The sample was divided into two groups: group 1 consisted of 49 men with HIV/AIDS who had condylomatous lesions or warts; group 2 consisted of 110

Table 1. Diagram of hierarchical analysis of the variables to control for confounding factors.

Level 1	• Number of subjects, age, education level, sexuality, number of partners in the last 3 months, condom use at last sex
Sociobehavioral data	• Use of alcohol, cigarettes and illicit drugs
Level 2	• Age at diagnosis, time since diagnosis, sexual acquisition, irregular cART use (<95% of intake drugs), age at first sexual intercourse
HIV-related data	• CD4+ T lymphocyte count and HIV load
Level 3	• Current or past carrier of hepatitis B, hepatitis C, syphilis, HSV and other STDs
Associated sexually transmitted diseases (STDs)	• Presence of one or more STDs
Level 4	• Number of therapeutic switches, including:
	nucleoside reverse transcriptase inhibitors
	non-nucleoside reverse transcriptase inhibitors
Data related to antiretroviral therapy of HIV/AIDS	protease inhibitors
	integrase inhibitors
	fusion inhibitors
	CCR5 co-receptor antagonists

Table 2. **Bivariate analysis of sociobehavioral data, history of sexually transmitted diseases and therapeutic regimen used by the 159 HIV patients studied.**

Variable	Group 1 (n=49)	Group 2 (n=110)	Total (n=159)	OR (95% CI)	p Value
n (%)	49 (31)	110 (69)	159 (100)	-	-
Age (years)[a]	44.6 ± 9.6	43.7 ± 10.2	44.0 ± 10.0	1.0 (0.9-1.0)	.61
Single[b]	11 (22)	56 (51)	67 (42)	0.5 (0.2-0.9)	**.04**
Up to 8 years of schooling[b]	26 (53)	44 (40)	70 (44)	1.7 (0.9-3.3)	.13
Homo- or bisexual[b]	14 (29)	43 (39)	57 (36)	0.6 (0.3-1.3)	.20
> 1 partner in 3 months[b]	9 (19)	8 (8)	17 (12)	2.7 (1.0-7.6)	**.05**
Condom use at last sex[b]	38 (78)	75 (69)	113 (72)	1.6 (0.7-3.4)	.26
Alcohol[b]	9 (18)	26 (24)	35 (22)	0.7 (0.3-1.7)	.46
Smoking[b]	24 (49)	55 (50)	79 (50)	1.0 (0.5-1.9)	.90
Illicit drugs[b]	6 (12)	11 (10)	17 (11)	1.3 (0.4-3.6)	.67
Hepatitis B[a]	12 (25)	23 (21)	35 (22)	1.2 (0.5-2.7)	.62
Hepatitis C[a]	11 (22)	23 (21)	34 (21)	1.1 (0.5-2.5)	.83
Syphilis[a]	7 (14)	15 (14)	22 (14)	1.1 (0.4-2.8)	.91
HSV[a]	10 (20)	8 (7)	18 (11)	3.3 (1.2-8.9)	**.02**
Therapeutic switches[a]	2 (3)	1 (2)	2 (2)	1.1 (0.9-1.3)	**.04**
NRTI[b]	44 (90)	95 (86)	139 (87)	1.4 (0.5-4.1)	.55
NNRTI[b]	34 (69)	80 (73)	114 (72)	0.9 (0.4-1.8)	.67
PI[b]	31 (63)	49 (45)	80 (50)	2.1 (1.1-4.3)	.06
II[b]	4 (8)	4 (4)	8 (5)	2.4 (0.6-9.8)	.25
FI[b]	4 (8)	2 (2)	6 (4)	4.8 (0.9-27.2)	.07
CCR5[b]	0 (0)	1 (1)	1 (1)	-	.99

[a]Mean ± SD; [b] n (%). 95% CI: 95% confidence interval. Group 1: patients with anogenital warts; group 2: patients without anogenital warts; STD: sexually transmitted diseases; cART: combination antiretroviral therapy; NRTI: reverse-transcriptase inhibitors; NNRTI: Non-nucleoside reverse-transcriptase inhibitors; PI: proteases inhibitors; II: integrase inhibitors; FI: fusion inhibitors; CCR5: chemokine receptor antagonists.

patients with HIV/AIDS without condylomatous lesions or warts.

Forty-nine (31%) of the 159 subjects studied were diagnosed with condylomatous lesions or anogenital warts and were included in group 1. The mean age of the patients was 44.0 ± 10.09 years. The sociobehavioral data and therapeutic regimens used are shown in Table **2**.

In bivariate analysis it was observed that two of socio-behavioral variables showed differences when comparing the two groups. Thus, there was a greater number of unmarried pacients in group 2 (p 0.04) and the number of individuals who reported more than one partner in the last 3 months was twice of group 1.

Analysis of previous diagnosis of sexually transmitted diseases (STDs) showed a higher prevalence of hepatitis B, followed by hepatitis C, syphilis and HSV, which were more frequent in patients of group 1, i.e., patients diagnosed with anogenital warts. However, only the frequency of infection with HSV differed between groups. There was a difference in the number of therapeutic switches, which was higher in patients with anogenital warts.

Regarding data related to HIV infection, no significant difference was observed between groups, in respect to CD4 + lymphocyte. Viral load was undetectable in 41.5% of the subjects, irrespective of the presence or absence of anogenital warts (data not shown), but this variable did not differ significantly between groups. The differences were found related to the time from diagnosis to inclusion in the study, Group 1 (with genital warts) have on average twice the time of diagnosis, and also had eight times greater chance of perform irregularly on cART compared to group 2 (Table **3**).

Multivariate logistic regression revealed a positive association between the presence of anogenital warts in patients infected with HIV and irregular cART and previous HSV (Table **4**).

DISCUSSION

Analysis of the set of data permitted the identification of sociobehavioral and clinical factors that, when combined, render men infected with HIV more vulnerable to the development of anogenital warts which are suggestive of HPV infection.

In the present study, the prevalence of homosexual or bisexual behavior was not higher among patients infected with HPV. No difference in the acquisition of HPV, here associated with the presence of anogenital warts, was observed between this population and heterosexual men, a

Table 3.   Bivariate analysis of HIV-related data of the 159 patients studied.

Variable	Group 1 (n=49)	Group 2 (n=110)	Total (n=159)	OR (95% CI)	p Value
Age at diagnosis (years)[a]	35 (11)	35 (13)	35 (13)	0.98(0.94-1.02)	.52
Time since diagnosis (years)[a]	10 (11)	5.5 (9)	7 (10)	1.06(1.00-1.12)	**.03**
Sexual acquisition[b]	25 (51)	72 (65)	97 (61)	0.6(0.3-1.1)	.09
Irregular cART use (<95% intake of drugs)[b]	9 (18)	3 (3)	12 (8)	8.02(2.06-31.14)	≤ **.01**
Age at first sexual intercourse (years)[a]	15 (3)	15 (3)	15 (3)	0.97(0.85-1.10)	.79
Viral load (copies/mm^3)[c]	52 (11591.5)	50 (3451.0)	50 (5392.0)	1.00(1.00-1.00)	.51
CD4+ T lymphocyte count (cells/mm^3)[c]	405 (361.8)	491 (396.0)	465 (336.0)	0.99(0.99-1.00)	.06

[a] Mean (SD); [b] n (%); [c] median (IQR). 95% CI: 95% confidence interval. Group 1: patients with anogenital warts; group 2: patients without anogenital warts.

Table 4.   Multivariate logistic regression analysis of factors associated with the presence of anogenital warts in patients with HIV/AIDS.

Variable	OR (95% CI)	p Value
Up to 8 years of schooling	1.51 (0.7 - 3.3)	0.29
Time since HIV diagnosis	1.03 (0.95 - 1.11)	0.46
Sexual acquisition	0.59 (0.27 - 1.30)	0.19
Irregular antiretroviral treatment	6.30 (1.48 - 26.89)	0.01
CD4+ T lymphocyte count	0.99 (0.99 - 1.0)	0.08
HSV	3.52 (1.11 - 11.14)	0.03
Protease inhibitors	1.69 (0.71 - 4.02)	0.23
Fusion inhibitors	1.78 (0.24 - 13.25)	0.57

Hosmer-Lemeshow test (p = 0.61); correct classification = 74.8%; Nagelkerke's R^2 = 0.32. 95% CI: 95% confidence interval. *p value ≤ 0.05.

finding also demonstrated by Baldwin *et al.* [12] and Costa *et al.* [13]. However, these authors investigated the presence of HPV rather than anogenital warts in other biological material (blood and urine), which wasn't studied in our researsh. Baldwin *et al.* [12] observed that 69.2% of homosexual or bisexual men were infected with HPV, a rate higher than the 29% found in the present study. It should be noted that the objective of this study was to determine the prevalence of genital warts and not the molecular diagnosis of HPV. This finding suggests that the population with an exclusively heterosexual behavior studied here takes little care or has attitudes that facilitate transmission of the virus. The vulnerability of heterosexual men has also been demonstrated by Masaka *et al.* [14] in a study of patients in Zambia, in which 56.8% of men reported to have unprotected sexual intercourse even after the emergence of genital ulcers. In Brazil, Figliuolo *et al.* [15] observed high rates of HPV in HIV positive male heterosexual population, probably due to the high rate of female infection in our population, demonstrated in study done by Côrrea *et al.* [16] conducted in Manaus, State of Amazonas, Brazil.

The transmission of STDs is intimately related to the number of sexual partners of the subject. In the present study, only 17 (12%) subjects reported to have had more than one sexual partner in the last 3 months prior to the interview. However, a difference was observed between the two groups, with the proportion of subjects reporting a larger number of sexual partners being higher in the group with anogenital warts (19%) compared to the group without genital lesions (8%). Similar results have been reported in most studies in which the multiplicity of sexual partners was a considerable risk factor for the acquisition of HPV, HIV and other STDs [17].

In this study among individuals who have been diagnosed with anogenital warts, 20.0% had coinfection with HSV while those without warts had only 7.0%. This difference was only significant among the STDs studied and increased in 3.5 times the chance of an individual with HIV be coinfected by HPV. This finding can be explained by the HSV be the most common cause of genital ulcer [18] and HPV as well as HIV and other STDs has a greater ease of dissemination in case of ulcerative lesions. HIV-infected men have high seroprevalence rates of HSV type II [19], according Mbwana *et al.* [20] that co-infection can result in increased bilateral transmission of virus since HIV has been isolated from virtually all genital ulcers in individuals co-infected with HSV. These same authors found 77.0 % of men who had genital ulcers were seropositive for HPV.

Condom use at last sex was regularly reported by the participants of this study, including 38 (78%) and 75 (69%) of patients with and without anogenital warts, respectively, with no difference between groups. This finding is unexpected, but agrees with the results reported in the study of Chadambuka *et al.* [17] in which condom use was a protective factor (odds ratio = 0.13) against the acquisition of

STDs among men in Zimbabwe, Africa. Suggesting that the presence of HPV was more associated with other variables and not necessarily with no condom use in the male population studied here. However, it is estimated that the use of condoms reduces HPV transmission by 70% to 80% [21].

Studies conducted on couples in India [22] and on men who have sex with men (MSM) in Italy [23] showed that after the diagnosis of HIV the subjects started to use condoms more frequently. This proportion increased from 15% to 92% among Indian couples and from 14% to 50% among MSM. These findings may explain the higher frequency of STD prevention after the diagnosis of HIV infection. According to Duarte *et al* [24]. in a study with women in Brazil, several reasons led to greater adherence to the use of condoms, as the fear of transmitting HIV to their uninfected partners and reinfection as well as from the acquisition of other STDs.

Irregular use of cART was reported by only 12 (8%) of the subjects studied. However, a significant difference was observed between groups, with the probability of this diagnosis being 6.3 times higher among patients with anogenital warts. According to Bärnighausen *et al*. [25], the incorrect use of cART can reduce immunity reflected in a decline of CD4+ T lymphocytes, thus facilitating the occurrence of other STDs.

Several studies have demonstrated the relationship of low CD4+ T lymphocyte counts and high HIV loads with increased HPV infection rates and development of anogenital warts [10, 26, 27]. These data were not found in the present study. Other factors that can render patients more susceptible to the development of anogenital warts and that worsen their immunological state include the lack of adherence to the therapeutic regimen and the development of resistance of HIV to available drug classes, events that are accompanied by a decrease in CD4+ T lymphocyte count, an increase in viral load and worsening of the patient's clinical status [28,29]. In addition to the immunological and clinical consequences of persistently high viremia, therapeutic failure also limits future treatment options [29].

In the present study, cART switches for therapeutic failure of HIV was associated with anogenital warts. This finding disagrees with the study of Chaturvetti *et al*. [9] in which irregular use of cART did not alter the prevalence, progression or regression of premalignant lesions, indicating the lack of restoration of specific immunity against HPV. In the same study, the authors evaluated the association between the use of cART and invasive cancers caused by HPV and observed that immune improvement increase the survival, which provided the time necessary for the development of premalignant or *in situ* lesions.

On the basis of the present results it can be concluded that anogenital warts occur in almost one-third of the male population infected with HIV and factors associated with a higher risk of being diagnosed with anogenital warts were irregular cART use and co-infection with HSV, other variables could not be associated.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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