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External genital warts in HIV-infected patients with sexually transmitted infections in Ibadan, Nigeria

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Abstract

Background: Human Papilloma Virus (HPV) infection in the genital area is usually asymptomatic, and when symptomatic, manifests in either benign or malignant forms. This study aims at providing information on the prevalence of external genital warts (EGWs) among people living with HIV (PLWHIVs) attending Antiretroviral Treatment (ART) clinic at the University College Hospital, Ibadan, Nigeria.

Methods: This is a descriptive cross-sectional survey of PLWHIVs attending ART clinic between January 2006 and December 2007. Diagnosis of genital warts was based on the findings of typical lesions on the external genitalia, vaginal, cervix or perianal region after clinical examination and informed consent from each participant. Antibodies against Herpes and HPV were measured using, Enzyme-linked immunosorbent Assay (ELISA).

Results: A total of 5,207 patients, 3519 female and 1688 males attended the ART clinic during the period. The mean age of the patients was 34.67 yrs (± 9.16). Five hundred and forty-two (10.0%) had various sexually transmitted infections (STIs). The prevalence of anogenital warts was 3.65% among the HIV-infected patients and 35.0 % among the subset of HIV- infected patients with STIs. The prevalence of genital warts was 1.5 times higher in treatment experienced patients (OR =1.46; 95%CI: 1.02, 2.10). Genital wart was found to be associated with low CD4 count, high viral load, treatment-experience and non-use of condom during sexual intercourse. (P = 0.002).

Conclusions: External genital warts are common among people living with HIV infection. According to the appropriate guidelines, HPV vaccine should also be offered to HIV-infected adolescents that are non-reactive to the virus.

Keywords: *External Genital warts, Human papilloma virus, HIV, Sexually transmitted infections*

Résumé

Contexte: L'infection par le virus du papillome humain (VPH) dans la région génitale est généralement asymptomatique et, lorsqu'elle est symptomatique, se manifeste sous forme bénigne ou maligne. Cette étude vise à fournir des informations sur la prévalence des verrues génitales externes (EGW) chez les personnes vivant avec le VIH (PVVIH) qui fréquentent une clinique de traitement antirétroviral (ART) à l'hôpital collège universitaire, Ibadan, au Nigeria.

Méthodes: Il s'agit d'une étude descriptive transversale des PVVIH fréquentant la clinique ART entre janvier 2006 et décembre 2007. Le diagnostic des verrues génitales était basé sur les résultats de lésions typiques sur l'organe génital externe, vaginal, cervical ou péri-anal après examen clinique et consentement informé de chaque participant. Les anticorps contre l'herpès et le VPH ont été mesurés en utilisant un dosage immunosorbant enzymatique (ELISA).

Résultats: Au total, 5 207 patients, 3519 femmes et 1688 hommes ont assisté à la clinique ART pendant la période. L'âge moyen des patients était de 34,67 ans (± 9,16). Cinq cent quarante-deux (10,0%) avaient des diverses infections sexuellement transmissibles (IST). La prévalence des verrues anogénitales était de 3,65% parmi les patients infectés par le VIH et de 35,0% parmi le sous-groupe de patients infectés par le VIH atteints d'IST. La prévalence des verrues génitales était 1,5 fois plus élevée dans le traitement expérimentés des patients (OR = 1,46; IC à 95%: 1,02, 2,10). On a constaté que la verrue génitale était associée à un faible taux de CD4, à une charge virale élevée, à une expérience de traitement et à la non-utilisation du préservatif pendant les rapports sexuels. (P = 0,002).

Conclusions: Les verrues génitales externes sont fréquentes chez les personnes vivant avec l'infection VIH. Selon les directives appropriées, le vaccin contre le VPH devrait également être offert aux adolescents infectés par le VIH qui ne sont pas réactifs au virus.

Mots-clés: *Verrues génitales externes, virus du papillome humain, VIH, infections sexuellement transmissibles*

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Introduction

Human papilloma virus (HPV) infection is one of the commonest sexually transmitted infections (STIs) worldwide among both men and women [1,2] with increasing incidence among men who have sex with men (MSM) (3). Genital Human Papilloma Virus (HPV) infection genital is frequently recognized as external genital warts (EGWs) in benign forms otherwise known as *condyloma acuminata* when symptoms are present [1,4]. EGWs may be fleshy, pedunculated, papular or macular lesions of the anal and/or genital mucosa and its adjoining areas of the body [4]. The lesions are filiform or sessile shaped. The warts can occur individually, in grape-like clusters, or form a cauliflower-like mass [4]

Majority of HPV infections are asymptomatic, transient, and usually resolve without causing clinical disease [1]. External genital warts are mostly linked to low risk HPV types 6 and 11 which have not been associated with anogenital cancers [4.5], though in rare occasions they are associated with Bushke-Lowenstein malignant tumours [6]. However, persistent infection with high-risk oncogenic types can progress to anogenital and oral cancers [7].. It has also been shown that women with previous history of EGWs have increased risk of cervical intraepithelial neoplasia (CIN) and cancer [2]. The true prevalence of HPV anogenital infection in the adult population has been found to be high (8, 9). Current evidence suggests that over 50 per cent of sexually active adults (15–25years of age) have been infected with one or more HPV types [7,10-12].. HPV is highly transmissible and transmission occurs most commonly through vaginal and anal intercourse [10,12-14]. First HPV infection is commonly acquired soon after sexual debut, even if exposure is limited to one sex partner [10, 11, 13] . The median time of development of the lesion after exposure has been estimated to be 5-6 months among women [15] and 11-12 months among men [16].

HIV infection and its associated immunosuppression are known to alter the course of HPV infection and its associated diseases [17,18]. The incidence of ano-genital and oral HPV infections among HIV – infected patients has been documented to increase progressively with the lowering of CD4 count [9, 19]. HIV infection among women has been found to be associated with an increased prevalence of cervical cancer precursors [19,20]. However, the co-infection with HPV could occur but this might not be sufficient to induce genital lesions [21]. In HIV-infected patients, external genital warts are more common, usually resistant to available treatment and more likely to recur than in general population [7, 9, 17, 22-24]. If the immune status of most of these patients are restored through effective therapy with Highly Active Retroviral Therapy (HAART), management of external genital warts are effective [24].

According to the meta-analysis conducted by Banura *et al* , the prevalence of EGWs varies from different regions of Africa [9]. Among sex workers and women with STIs, the prevalence ranges from 3.5-10.5% in West Africa, 3.3-10.7% in the East and 2.4-14.0% in Central and southern Africa [9]. The prevalence is lower among sexually active men in all regions(9). However, HIV positivity has been found to be a risk factor for acquisition of HPV infections and the prevalence is significantly higher in HIV – infected adult population [25]. The clinical evaluation of the burden of genital warts especially among women and men with the advent of HIV infection in the tropics needs to be reviewed regularly.

The objective of this study was to determine the prevalence and burden of anogenital warts among the subset of HIV-infected patients attending ART clinic at the University College Hospital, Ibadan, Nigeria.

Methods

This is a descriptive cross-sectional survey of 5,207 patients attending the antiretroviral clinic of the University College Hospital (UCH), Ibadan between the periods of January 2006 and December 2007. UCH is a tertiary health facility in Ibadan, southwestern, Nigeria. The adult ART clinic is one of the Government of Nigeria HIV clinics with support, through AIDS Prevention Initiative in Nigeria (APIN) and Harvard University, by President's Emergency Plan for AIDS Relief (PEPFAR) Program.

As part of the evaluation at enrolment and under aseptic conditions, physicians inspect the perineum /genitalia for signs of STIs. Diagnosis of genital warts was based on the clinical findings of typical lesions as previously described by Okesola & Fawole, Ekweozor *et al* and Lacy *et al* [4, 12, 26] on the external genitalia, penile shaft, vaginal, cervix or perianal region. Urethral swabs were taken from males as well as High vaginal swabs (HVS) and endocervical swabs (ECS) from females for microscopy and culture to establish diagnosis of other associated STIs from the patients with suspected STIs. About 5-10ml of venous blood was collected aseptically from each patient into EDTA bottle and tested for HPV IgG antibody and herpes simplex virus (HSV) IgG antibody. The detection of

HSV IgG was done using the 3rd generation enzyme-linked immunosorbent assay (ELISA) while ELISA test kits by DIAPRO Diagnostics Bioprobes Milano-Italy were used to tests the plasma samples for HPV IgG antibodies according to the manufacturer's instruction. The measurement of CD4 + T lymphocyte (CD4) count was carried out by flow cytometry. Roche Ampiclor RNA PCR assay was used for the measurement of plasma HIV RNA (viral load). Risky sexual behavior was defined as non-use or inconsistent use of condom.

Ethical considerations

The Antiretroviral Treatment program was approved by the University of Ibadan/University College Hospital Ibadan Joint Institutional Review Board. Informed consent forms were signed by all patients during enrollment procedures. Pictures were also taken on few occasions after informed consent.

Data analysis

Statistical Analysis was performed with the Statistical Package for Social Sciences (SPSS) version 20. Continuous variables were presented as mean and standard deviation while categorical variables were presented as frequencies / percentages. Associations between categorical variables were investigated using Chi square test, while student's t-test was used to test for significant difference in continuous variables. P value was set at 5%.

Results:

Demographic and clinico-pathological presentations

A total of 5,207 patients, 3519 female and 1688 males attended the ARV clinic during the period with mean age of 34.67 years (SD= 9.16; range 19-77years). Two thousand five hundred and sixty-seven (2,567, 49.3%) were in the 30-39 year age range. Three thousand and seventy-two (3,072, 59.0%) of the patients evaluated were married. Table 1 is a summary of the socio-demographic status of the patients. Five hundred and forty two patients had at least one STI based on history and examination at baseline. The prevalence of STIs among the patients evaluated was 10.4%, 12.42% (437 of 3519) in females and 6.22% (105 of 1688) among the males. The male to female ratio of those patients with various STIs was 1: 4.

External genital warts were diagnosed in 3.65% (190 of 5,207) of the HIV-infected patients. The prevalence of external genital warts among the subset of patients with STIs was 35.1% (190 of 542).

Table 1: Socio-demographic characteristics and treatment status of the patients

Characteristics	Frequency (N=542)	Percentage (%)
Age categories		
10-19	1	0.2
20-29	143	26.4
30-39	267	49.2
40-49	87	16.0
50-59	28	5.2
60-69	15	2.8
70-79	1	0.2
Level of Education		
None	38	7.0
Primary	160	29.5
Secondary	215	39.7
Tertiary	129	23.8
Marital Status		
Single	86	15.9
Married	320	59.0
Separated	51	9.4
Divorced	25	4.6
Widowed	60	11.1
Sex		
Male	105	19.4
Female	437	80.6
Treatment status		
Naïve	241	44.5
Experienced	301	55.5

All the patients diagnosed with EGW were positive to HPV IgG antibody. Of the 190 cases of external genital warts, one hundred and fifty-two (80.0%) were females while 38 (20.0%) were males giving male to female ratio of 1: 4.2. The external genital wart lesions were found on both adolescents and adults. The sites of the EGWs in females included the vulva, vagina, perineum and perianal region (Figures 1 and 2). In males, warts were mostly found on the glans penis, shaft of the penis, perineum, suprapubic and anal regions (Figure 3). Two of the male patients with EGWs had florid anal warts. The mean duration of the external genital warts prior to presentation was nine months (Range: 3months-2 years). Four hundred and sixty one patients (85.0%) usually engage in heterosexual relationship while two of the males admitted having sex with males.

Two hundred and twenty-three women who had STIs at presentation (223/437, 41.1%) had vulvo-vaginal candidiasis, 115 (21.3%) had herpes genitalis, two (0.4%) had gonorrhoea while one

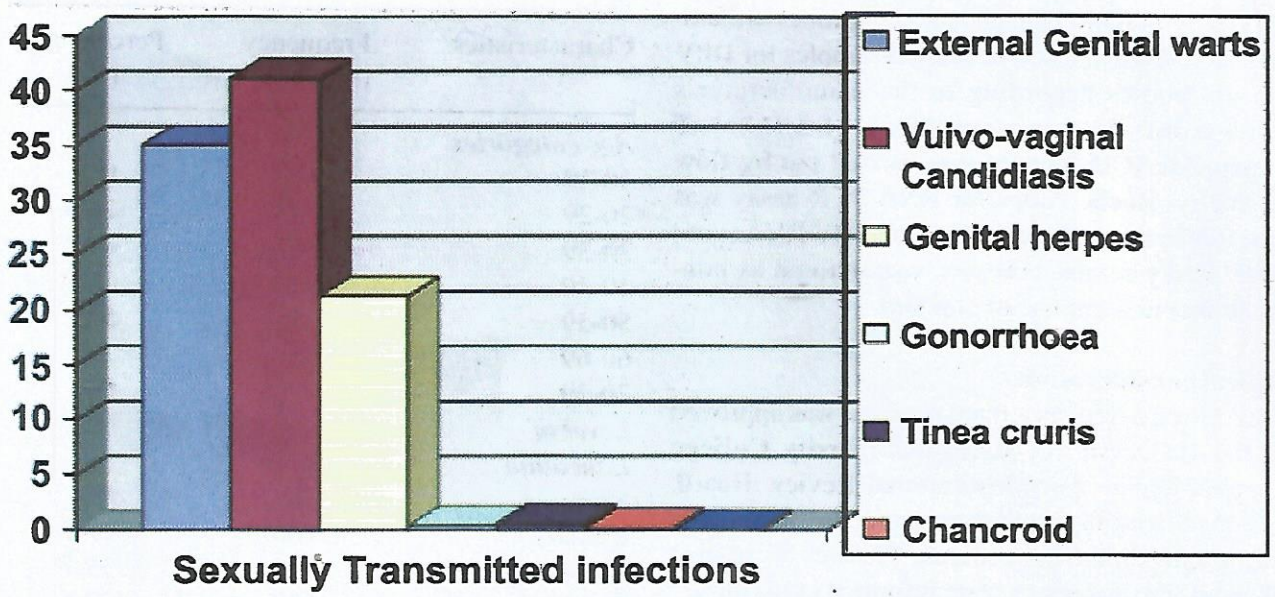

Fig. 1: Distribution of sexually transmitted infections among the PLWHIV in Ibadan

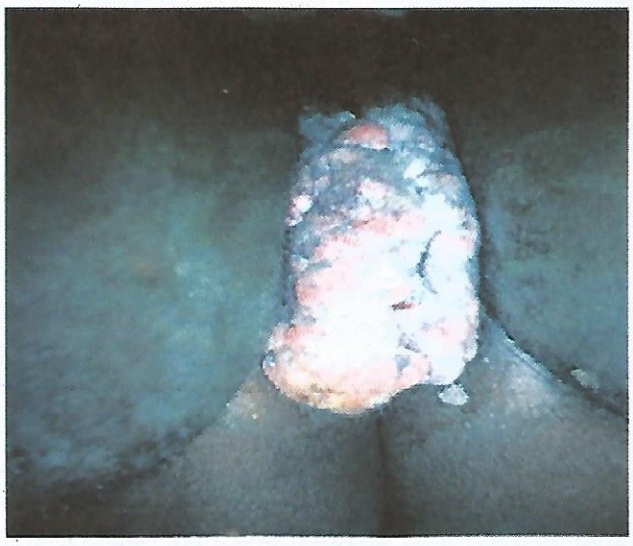

Fig. 2: Giant Vulva warts

Fig. 4: Genital warts in male

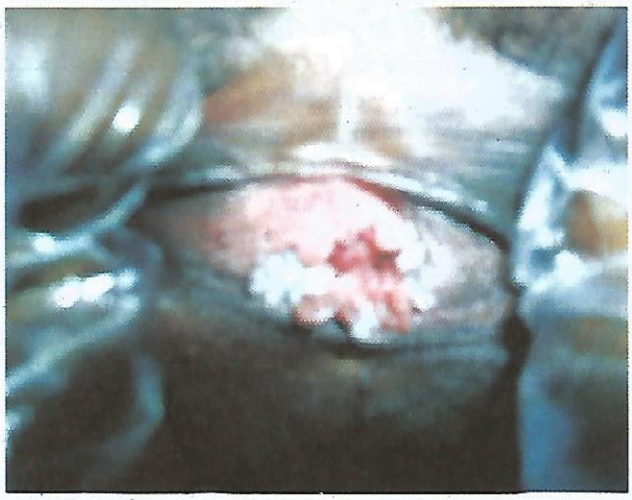

Fig. 3: Intra-vaginal warts

(0.2%) had *Molluscum contagiosum* virus infection as shown in Figure 4. Twenty (3.69%) of them who presented with STIs had EGWs co-infection. The common co-infections in the evaluated population of patients were vaginal candidosis and EGWs (9, 1.66%), as well as genital herpes and EGWs (7, 1.29 %). Two hundred and forty-seven (45.6 %) of those with STIs were HAART naive. Prevalence of EGW was found to be higher among the married (63.2%), and secondary school leavers (42.1%).

Most of the patients who were unwilling to have protected sexual intercourse (140/392, 35.7 %) had higher prevalence of genital warts compared to those who reported condom use (50/150, 33.3%), though not significantly associated (P>0.05).

Table 2: Association of social demographic and clinical correlates with prevalence of genital warts

Characteristics	Genital Warts Yes (n=190)	No (n=352)	P values	OR (95% CI)
Sex				
Male	38 (20.0%)	67 (19.0%)	0.786	1.06 (0.68 -1.66)
Female	152 (80.0%)	285 (81.0%)		
Condom Use				
Yes	50 (26.3%)	100 (28.4%)	0.603	0.9 (0.61-1.34)
No	140 (73.7%)	252 (71.6%)		
Treatment status				
Naive	73 (38.4%)	168 (47.7%)	0.037	1.46 (1.02-2.10)
Experienced	117 (61.6%)	184 (52.3%)		
Age				
10-19	1 (0.5%)	0 (0.0%)	0.185	
20-29	53 (27.9%)	90 (25.6%)		
30-39	99 (52.1%)	168 (47.7%)		
40-49	25 (13.2%)	62 (17.6%)		
50-59	10 (5.3%)	18 (5.1%)		
60-69	2 (1.0%)	13 (3.7%)		
70-79	0 (0.0%)	1 (0.3%)		
Level of Education				
None	8 (4.2%)	30 (8.5%)	0.46*	
Primary	59 (31.1%)	101(28.7%)		
Secondary	80 (42.1%)	135 (38.4%)		
Tertiary	43 (22.6%)	86 (24.4%)		
Marital status				
Single	30 (15.8%)	56 (15.9%)	0.361	
Married	120 (63.2%)	200 (56.8%)		
Divorced	10 (5.3%)	15 (4.3%)		
Separated	13 (6.8%)	13 (6.8%)		
Widowed	17 (8.9%)	43 (12.2%)		
CD4 group	N=145	N=266		
<200	89 (61.4%)	183(68.8%)	0.164	
201-350	27(18.6%)	48(18.0%)		
>350	29(20.0%)	35(13.2%)		

**P value obtained from Chi square test for trend.*

Analysis of viral load and CD4 counts

Out of the 542 PLWHAs with STIs, one hundred and fifty (27.7%) reported condom use, Eighteen (3.3 %) had viral load < 200 copies/ ml while 272 (50.1 %) had low CD4 count (< 200 cells / mm3.) The mean log viral load was 5.02 $\pm$ 0.94. The prevalence of external genital warts was 1.5 times higher in treatment experienced patients compared to those that are HAART naïve. (OR =1.46; 95%CI: 1.02, 2.10) as shown in Table 2.

External genital wart was also found to be higher in patients with low CD4 count (89/190, 61.9%), high viral load (129/136, 94.9%) and unwillingness to have protected sexual intercourse (140/190, 73.7%) (P >0.05), though not significantly associated (Table 2).

Discussion

HIV infection and its associated immunosuppression are known to alter the course of HPV infection and its associated diseases [17, 18] . In the early 1990s, the rate of reported cases of genital warts was found to be scanty [12]. Our study has demonstrated a lower rate (3.65%) of external genital warts among the patients enrolled in antiretroviral clinic, University College Hospital, Ibadan, Nigeria. Previous studies

have confirmed rates ranging from 8-42% depending on methods of diagnosis that includes visible anogenital warts, cytopathology and viral DNA for the molecular diagnosis of HPV [12, 23, 26]. Our finding is also much lower than 7.0 % obtained in a previous study conducted in Burkina Faso [23]. However, the prevalence of EGW was found to be 35.0% among the subsets of patients diagnosed with sexually transmitted infections. This is within the range of the findings of the previous studies [24, 27]. The increased prevalence observed among these cohorts of patients might not be unconnected with the recrudescence of previously latent HPV infection in those who are sexually active, while others may have been as a result of new infections.

External genital wart has been found to be common among young sexually active female gender with multiple sexual partners [7, 10-12]. This has been demonstrated in our study that shows female to male infection ratio to be 4:1. In a study by Thompson *et al*, the incidence of EGW was found to be higher in females than males prior to year 2000 [27]. However, the incidence was found to be increasing steadily among males from 2000 to 2011(27). Contrary to disproportionately higher genital warts in MSM in the study conducted by Jiamton *et al* [3], anogenital warts were higher in females living with HIV / AIDS in our centre from our study. Young adults especially the married women within the age bracket of 30-39 years were noted to be the highest risk group with the rate of 49.3%. This is closely followed by the most sexually active group aged between 20-29years with the rate of 26.4%. This is contrary to what was obtained in similar studies among sexually active adults where the peak age incidence of adults with EGW was between 20-29 years [12, 26]. These findings from our study may not be unconnected with the late presentations of young women at the ART clinic who might have been infected when they were younger. The various sites of EGW as noted on the vulva, mons pubis, inguinal folds, glans penis, shaft of the penis, scrotum and coronal sulcus in this study are similar to the findings in other studies [14, 28].

Genital herpes (21.3%) was found to be the most sexually transmitted co-infection in both male and female patients in our study while vulvo-vaginal candidiasis (41.1%) is the most common sexually transmissible disease co-infection among women especially in middle-aged group. This observation is in agreement with the findings in similar studies [12, 23, 26, 28, 29], though the rate of co-infections was lower than what we have from our findings.

Since anogenital HPV related disease is related to immunosuppression, it could be expected that the clinical epidemiology of HPV infection may change as a result of HAART-associated reversals in immunosuppression. Prevalence of genital warts was 1.5 times higher among the treatment experienced patients than HAART naïve patients. This might be explained by the fact that at the time the study was conducted; only those with significant immunosuppression were placed on treatment while those with high CD4 counts were monitored serially until their CD4 count dropped below a certain threshold (350cells/mm^3). This meant that in general, being on ART meant that the patient had a lower CD4 count and thus more immunosuppressed. This result is contrary to the previous findings and reviews which believed that clinical management of genital warts would be easier with effective HAART [24]. However, our finding is in agreement with what was obtained by Low *et al* who reported that antiretroviral therapy was not protective against the persistence of genital warts in HIV-infected patients [23].

Majority of the infected patients who reported non-use of condom during sexual intercourse were noted to have higher prevalence of genital warts (73.7%) than those that reported condom use. The finding is in agreement with the finding of meta-analysis conducted by Manhart and Koutsky, [30] who reported that the available data could not provide a precise estimate of prevention of genital HPV infection due to inconsistency, but they however suggested that condom may not prevent HPV infection but could protect genital warts [30]. Risky sexual behavior was found to be significantly associated with low level of education ($P<0.0001$). This result is in agreement with the findings of Soori *et al*, 2013 [29] and more often transmission has been reported from female partners to male partners than from male to female [31]. In this study, external genital wart was also associated with low CD4 count, high viral load, treatment-experienced and non-use of condom during sexual intercourse. ($P = 0.002$).

Most of our patients (133/190, 73.7%) were treated with 20% podophyllin in a tincture of benzoin with complete resolution of their lesions. However, there are many treatment options that are currently being adopted for external genital warts in different part of the world [12, 26, 28, 32], with wide variation across many sites depending on the budget and policies [28]. Some of the treatment options include 5% imiquimod, cryotherapy, electrosurgical resection, interferon alpha-2b and electro fulguration [28]. Combination of interferon alpha-2b and electro

fulguration has been found to be highly effective for children with massive genital warts [28]. Those with extensive intravaginal warts were referred to the gynecological clinic for further management. Two of our patients who were offered surgical resection had a complete resolution of their lesions.

Conclusions and recommendation

Preventive program is mandatory for anogenital warts, especially among this group of patients. Full screening for CIN remains necessary in HIV-positive women and it is likely that screening for AIN will be beneficial as well to prevent invasive anogenital cancer in long-term AIDS survivors(20). Diagnosis and treatment of genital warts as well as follow-up of HIV-infected patients should be performed routinely in the HIV clinics. PLWHIVs should be counseled on practices that may reduce the risk of acquiring HPV infection, including safe sexual practices and reduction in number of sexual partners. Screening for genital warts and follow-up of HIV-infected patients should be performed routinely. According to the appropriate guidelines, HPV vaccine should also be offered to HIV-infected adolescents using appropriate guidelines.

HIV-infected persons in care may be an important target group in which to conduct regular screening for Sexually Transmitted Infections (STIs) to prevent enhanced transmission of HIV.(1) Pap smear screening for cervical dysplasia and cancer in women with HIV infection should be more frequent than routinely recommended for the general population and requires careful follow-up. HPV testing of pap smear samples where facilities exist should be performed to detect infection even before it has been present long enough to cause cervical or other anogenital abnormalities. Widespread HPV vaccination could make an important reduction to morbidity and mortality related to HPV infection in developing countries like Nigeria. The quadrivalent HPV types 6, 11, 16 and 18 recombinant vaccine is highly immunogenic and is highly recommended. The possibility of making the vaccine available to adolescent boys and men should also be considered to help break the cycle of widespread HPV infection.

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References

1. Lacey CJ. Therapy for genital human papillomavirus-related disease. Journal of Clinical Virology. 2005;32:82-90.
2. Kjær SK, Nam TT, Sparen P, *et al*. The burden of genital warts: a study of nearly 70,000 women from the general female population in the 4 Nordic countries. Journal of Infectious Diseases. 2007;196(10):1447-1454.
3. Jiamton S, Leeyaphan C, Maneeprasopchoke P and Omcharoen V. Prevalence and clinical manifestations of male patients with anogenital warts attending a sexually transmitted disease clinic prior hpv vaccine recommendation. The Southeast Asian journal of tropical medicine and public health. 2014;45(6):1337-1343.
4. Lacey CJ, Lowndes CM and Shah KV. Burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. Vaccine. 2006;24:S35-S41.
5. Koutsky LA, Galloway DA and Holmes KK. Epidemiology of genital human papillomavirus infection. Epidemiologic Reviews. 1988;10:122.
6. Giuliano AR, Tortolero-Luna G, Ferrer E, *et al*. Epidemiology of human papillomavirus infection in men, cancers other than cervical and benign conditions. Vaccine. 2008;26:K17-K28.
7. Laxmisha C, Thappa DM and Jaisankar TJ. Viral warts-A clinico-epidemiological study. Indian Journal of Dermatology. 2003;48(03):142.
8. Blas MM, Brown B, Menacho L, *et al*. HPV Prevalence in Multiple Anatomical Sites among Men Who Have Sex with Men in Peru. PloS one. 2015;10(10):e0139524.
9. Banura C, Mirembe FM, Orem J, *et al*. Prevalence, incidence and risk factors for anogenital warts in Sub Saharan Africa: a systematic review and meta analysis. Infectious agents and cancer. 2013;8(1):27.
10. Burchell AN, Winer RL, de Sanjosé S and Franco EL. Epidemiology and transmission dynamics of genital HPV infection. Vaccine. 2006;24:S52-S61.
11. Grant LA, Dunne EF, Chesson H and Markowitz LE. Considerations for human papillomavirus (HPV) vaccination of mid-adult women in the United States. Vaccine. 2011;29(13):2365-2370.
12. Ekweozor CC, Adeyemi-Doro FA, Ashiru JO and Osoba AO. Anogenital warts in patients attending the sexually transmitted diseases clinic in Ibadan, Nigeria. African journal of medicine and medical sciences. 1994;23(4):311-314.

13. Woodman CB, Collins S, Winter H, *et al.* Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. The Lancet. 2001;357(9271):1831-1836.
14. Schiffman M and Kjaer SK. Natural history of anogenital human papillomavirus infection and neoplasia. J Natl Cancer Inst Monogr. 2003;31:14-19.
15. Garland SM, Steben M, Sings HL, *et al.* Natural history of genital warts: analysis of the placebo arm of 2 randomized phase III trials of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine. Journal of Infectious Diseases. 2009;199(6):805-814.
16. Arima Y, Winer RL, Feng Q, *et al.* Development of genital warts after incident detection of human papillomavirus infection in young men. Journal of Infectious Diseases. 2010;202(8):1181-1184.
17. Palefsky JM, Holly EA, Ralston ML and Jay N. Prevalence and risk factors for human papillomavirus infection of the anal canal in human immunodeficiency virus (HIV)-positive and HIV-negative homosexual men. Journal of Infectious Diseases. 1998;177(2):361-367.
18. Chin-Hong PV and Palefsky JM. Natural history and clinical management of anal human papillomavirus disease in men and women infected with human immunodeficiency virus. Clinical Infectious Diseases. 2002;35(9):1127-1134.
19. Palefsky J. Biology of HPV in HIV infection. Advances in dental research. 2006;19(1):99-105.
20. de Sanjosé S and Palefsky J. Cervical and anal HPV infections in HIV positive women and men. Virus research. 2002;89(2):201-211.
21. Goncalves MA, Burattini MN, Donadi EA and Massad E. Risk factors associated with genital warts in HIV-positive Brazilian women. Tumori. 2003;89(1):9-15.
22. De Panfilis G, Melzani G, Mori G, Ghidini Aand Graifemberghi S. Relapses after treatment of external genital warts are more frequent in HIV-positive patients than in HIV-negative controls. Sexually transmitted diseases. 2002;29(3):121-125.
23. Low AJ, Clayton T, Konate I, *et al.* Genital warts and infection with human immunodeficiency virus in high-risk women in Burkina Faso: a longitudinal study. BMC infectious diseases. 2011;11:20.
24. Klausner JD and Kent CK. HIV and sexually transmitted diseases. Latest views on synergy, treatment, and screening. Postgraduate medicine. 2004;115(4):79-84.
25. Silverberg MJ, Ahdieh L, Muñoz A, *et al.* The impact of HIV infection and immunodeficiency on human papillomavirus type 6 or 11 infection and on genital warts. Sexually transmitted diseases. 2002;29(8):427-435.
26. Okesola AO and Fawole OI. Prevalence of human papilloma virus genital infections in sexually transmitted diseases clinic attendees in Ibadan. West African journal of medicine. 2000;19(3):195-199.
27. Thompson LH, Nugent Z, Blanchard JF, Ens C and Yu BN. Increasing incidence of anogenital warts with an urban-rural divide among males in Manitoba, Canada, 1990-2011. BMC public health. 2016;16:219.
28. Pirotta MV, Stein AN, Fairley CK, *et al.* Patterns of treatment of external genital warts in Australian sexual health clinics. Sexually transmitted diseases. 2009;36(6):375-379.
29. Soori T, Hallaji Z and Noroozi-Nejad E. Genital warts in 250 Iranian patients and their high- risk sexual behaviors. Archives of Iranian medicine. 2013;16(9):518-520.
30. Manhart LE and Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia?: A meta-analysis. Sexually transmitted diseases. 2002;29(11):725-735.
31. Park IU, Introcaso C and Dunne EF. Human Papillomavirus and Genital Warts: A Review of the Evidence for the 2015 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2015;61 Suppl 8:S849-55.
32. Suarez-Ibarrola R, Heinze A, Sanchez-Sagastegui F, *et al.* Giant Condyloma Acuminatum in the Genital, Perineal and Perianal Region in a Pediatric Patient. Literature Review and Case Report. Urology case reports. 2016;7:14-16.