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Short Communication

High Risk Human Papillomavirus Persistence Among HIV-infected Young Women in South Africa

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SUMMARY

Objectives: Persistence of infection with high-risk Human papillomaviruses (HR-HPV) increases the risk of incident and progressive precancerous lesions of the cervix. Rates of HR-HPV persistence have been shown to be increased among HIV-infected adult women, however there is a paucity of literature addressing HPV persistence in the young HIV-infected population. We compared rates of HR-HPV persistence between HIV-infected and HIV-uninfected young women.

Methods: We obtained self-collected vaginal swabs at six-month intervals from 50 HIV-uninfected and 33 HIV-infected young women recruited through a community youth center (age 17-21 years) and compared rates of HR-HPV persistence. HR-HPV testing was conducted using the Roche's Linear Array® HPV Test.

Results: Eighty-three prevalent (upon baseline testing) and incident (upon subsequent testing) individual HR-HPV infections were identified among 43 members of the cohort (23 HIV-uninfected and 20 HIV-infected). At twelve months, 19% of baseline HR-HPV infections continued to be present with a statistically significant difference between HIV-uninfected and HIV-infected participants (4% versus 31%; p=0.01).

Conclusions: HIV-infected young women in our cohort had a seven-fold increased rate of persistence of HR-HPV overall at 12 months, indicating an increased risk for incident and progressive precancerous lesions. Identification of persistent infection with HR-HPV may complement cytological findings in determining the need for colposcopy.

1. Introduction

High-risk Human papillomaviruses (HR-HPV) cause cervical cancer[1,2]. While most infections with HR-HPV are transient[3] some may persist for six months or longer. Persistence of infection with HR-HPV is associated with increased incidence of precancerous squamous intraepithelial lesions (SILs) of the cervix[4], decreased rates of regression of SILs[5], increased rates of progression of SILs[6], and increased risk of invasive cervical cancer[7].

Invasive cervical cancer is an AIDS-defining illness[8]. Infection with HIV significantly impacts the natural history of HPV infection. Among HIV-infected women, rates of persistent HR-HPV infection are increased multifold[9]. HIV-infected young women are physiologically and behaviorally different than adults, and the impact of HIV on persistence of HR-HPV infections in this age group is understudied. The aim of the present study was to compare rates of HR-HPV persistence between HIV-infected and HIV-uninfected young women recruited through a community youth center.

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2. Methods

Between October 2012 and January 2014, we enrolled 50 HIV-uninfected and 33 HIV-infected sexually active South African females age 17-21 years (M = 19.06 years; S.D. = 1.48; IQR = 18.00 – 20.00) into a longitudinal study in which self-collected vaginal swabs for HPV DNA analysis were obtained at six-month intervals. Study participants were enrolled through a youth community center in Masiphumelele, a township in Cape Town, South Africa. All participants signed informed consent (age 18 years and older) or signed adolescent assent documents (age 17 years) to accompany parental consent forms. This study was approved by the Research Subjects Review Board at the University of Rochester and the Human Research Ethics Committee at the University of Cape Town.

For self-sampling, patients were instructed to insert a Dacron® swab high into the vagina and twirl it for 10 seconds. Self-sampling was conducted in private. Samples were stored in Digene transport medium, and DNA was extracted using the MagNA Pure Compact Nucleic Acid Isolation Kit (Roche Diagnostics). HPV genotyping was conducted using Roche's Linear Array® HPV Test. This kit detects 37 HPV genotypes including all oncogenic HPV types identified by the International Agency for Research on Cancer (IARC)[2]. We defined HR-HPV to include the 13 genotypes designated by IARC to have sufficient evidence to cause cervical cancer (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) and to have strong mechanistic evidence for cervical cancer (type 68)[2].

All prevalent HR-HPV infections identified upon baseline testing and all incident HR-HPV infections identified upon subsequent testing were assessed for type-specific HR-HPV persistence. Persistence was defined as presence of type-specific HR-HPV DNA in (a) both components of any sequential pair of specimens (e.g., t1 and t2) or (b) both components of any pair of specimens collected 12 months apart (e.g., t2 and t4). Chi-square tests for independence were used to examine overall and type-specific differences in persistence between HIV-uninfected and HIV-infected participants (Table 1).

3. Results

Eighty-three prevalent (upon baseline testing) and incident (upon subsequent testing) individual HR-HPV infections were identified among 43 members of the cohort (23 HIV-uninfected and 20 HIV-infected). The other 40 members of our cohort (27 HIV-uninfected and 13 HIV-infected) tested negative for HR-HPV throughout the study period. Overall, 27% of these infections were persistent at six months (21% among HIV-uninfected and 33% among HIV-infected, p=0.23). At twelve months, 19% of baseline HR-HPV infections continued to be present with a statistically significant seven-fold difference in persistence between HIV-uninfected and HIV-infected participants (4% versus 31%; p=0.01). Rates of persistence across HIV status are summarized in Table 1.

HIV-infected youth were slightly older (mean age 19.91 years, SD = 1.13) than HIV-uninfected youth (mean age 18.44 years, SD = 1.40), $p<0.05$, however, there was no difference in number of lifetime sexual partners or number of sexual partners in the last six months across HIV status. The average CD4 count among all HIV-infected participants was 471/mm^3 (IQR= 395 - 508; CD4 counts were not available for 6 participants). Nine of the 33 HIV-infected participants in our cohort were on anti-retroviral therapy (ART). Use of ART and CD4 count were not found to be significantly associated with HR-HPV infection.

The overall incidence rate of HR-HPV infection among study participants without HR-HPV infection upon baseline testing was found to be 743 new HR-HPV infections per 100 person-years. Similar rates of persistence were found for vaccine genotypes (HPV 16 and 18) and non-vaccine high-risk genotypes. All 13 HR-HPV genotypes were found among our cohort upon initial testing. At baseline, types 16, 52, and 68 were most commonly identified. At six months, types 16, 39, and 45 were most likely to found to be persistent, and at 12 months types 16 and 52 were most likely found to be persistent. Due to inadequate power we did not identify statistically significant differences in type-specific persistence between groups.

Table 1
Comparing HR-HPV Persistence Across HIV Status

	HIV Positive n (%)	HIV Negative n (%)	p – value[a]
6 Month Follow-up			
All HR-HPV Persistent	16 (33%)	7 (21%)	$p=0.23$
Cleared	33 (67%)	27 (79%)	
HPV16 or 18 Persistent	4 (40%)	2 (29%)	$p=0.63$
Cleared	6 (60%)	5 (71%)	
Non-Vaccine HR-HPV Persistent	12 (40%)	5 (29%)	$p=0.26$
Cleared	27 (60%)	22 (71%)	
12 Month Follow-up			
All HR-HPV Persistent	9 (31%)	1 (4%)	$p=0.01$
Cleared	20 (69%)	24 (96%)	
HPV16 or 18 Persistent	3 (38%)	0 (0%)	$p=0.07$
Cleared	5 (63%)	7 (100%)	
Non-Vaccine HR-HPV Persistent	6 (29%)	1 (6%)	$p=0.06$
Cleared	15 (71%)	17 (94%)	

[a] p-values based on Pearson χ^2 with 1 degree of freedom (2 X 2 analyses).

4. Discussion

HIV-infected young women in our cohort had a seven-fold increased rate of persistence of HR-HPV overall at 12 months, indicating an increased risk for incident and progressive precancerous lesions. Although CD4 counts among the HIV-infected young women in our cohort were relatively high, the increased risk of HR-HPV persistence compared to their HIV-uninfected counterparts highlights the importance of immune control of HPV infection.

Identification of persistent infection with HR-HPV may complement cytological findings in determining the need for colposcopy. Although HPV DNA testing is currently recommended only for older women without HIV infection[10], it may contribute to optimal cervical cancer screening among young HIV-infected women given their increased risk for invasive cervical cancer.

Our study is limited by a modest sample size and relatively brief follow-up period. Enlargement and further follow-up of this cohort with additional serial HPV DNA testing and cervical cytology testing will provide greater insight into the relationship between HR-HPV persistence and the incidence and progression of SILs in HIV-infected young women.

Conflict of Interest Statement: None of the authors have a conflict of interest to disclose.

Ethical Approval: This study was approved by the Research Subjects Review Board at the University of Rochester and the Human Research Ethics Committee at the University of Cape Town.

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