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High-Grade Cervical Disease in Adolescents With HIV

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Abstract

Objective—To estimate the risk of high-grade squamous intraepithelial lesions (HSIL) in adolescents with HIV.

Materials and Methods—Review of cervical cytology and biopsy results from women aged 20 years and younger obtained within 3 years of enrollment in a prospective multicenter study.

Results—At enrollment, none of 132 adolescent participants (45 HIV seropositive and 87 seronegative) had HSIL or cervical intraepithelial neoplasia grade 2 or 3 (CIN 2,3). Eight (7%) of 123 women with follow-up developed high-grade disease after a median of 2.6 years of observation. The incidence of HSIL/CIN 2,3 was 2.7/100 person-years (4.8/100 person-years in HIV seropositive and 1.6/100 person-years in HIV seronegative women; relative risk = 3.1; 95% CI = 0.76–12.74; $p = .13$). No cancers were found in adolescents during the study.

Conclusions—The low incidence of HSIL or CIN 2,3 in adolescents suggests that optimal management is careful observation rather than preventive treatment of low-grade abnormalities.

Keywords

HPV; adolescents; cervical cancer prevention; Pap test; HIV in women

Women with the HIV have higher rates of infection with genital types of the human papillomavirus (HPV), of carcinogenic HPV infection, and of cervical cancer precursors than women without HIV. In a large US multicenter cohort study of HIV-infected women, the prevalence of Pap abnormality was 38% [1], and 73% of HIV-infected women had developed at least 1 Pap abnormality after 5 years of follow-up [2]. However, progression to cervical cancer seems to be uncommon, at least among women in a cancer prevention program [3].

Human papillomavirus infections are especially common in young women [4,5]. On the other hand, young women's ability to clear HPV [6,7] and low-grade squamous intraepithelial lesions (SILs) is also high [8], so few have persistent infections. In fact, the high regression rate of HPV and SIL in women aged 20 years and younger recently prompted the development of guidelines for management of abnormal Pap tests in this group [9]. The new guidelines suggest that after a cytology result of atypical squamous cells of undetermined significance (ASCUS) and low-grade SIL (LSIL), young women should be followed annually without colposcopy unless results of Pap tests are persistently abnormal. Whether these guidelines are applicable to young women with HIV is unclear.

We reported that young women with HIV are more likely to have prevalent abnormal Pap test results and are more likely to develop incident Pap abnormalities than their older counterparts [1,2]. Similar disparities were reported in the Reaching for Excellence in Adolescent Care and Health (REACH) study, which also found that 22% of women aged 15–18 years with HIV progressed to high-grade SIL (HSIL) over up to 4 years of observation, compared with only 5% of young women without HIV [10]. This suggests that cancer risk is high in these young women, and colposcopy rather than observation is needed when young women with HIV have abnormal Pap test results. The increased rate of HSIL found in REACH has not been replicated. We set out to determine the prevalence and incidence of HSIL in 45 HIV-seropositive and 87 HIV-seronegative women aged 20 years and younger.

MATERIALS AND METHODS

This investigation was part of the Women's Interagency HIV Study (WIHS), an ongoing multicenter prospective cohort study of the natural history of HIV infection and related health conditions among HIV-seropositive women and at-risk HIV-uninfected comparison women. The protocols, recruitment processes, procedures, and baseline results of the WIHS have been previously described; seropositive WIHS participants are representative of US women with HIV [11]. Women's Interagency HIV Study enrollment began in 1994 at 6 study consortia (Brooklyn; Bronx; Chicago; Los Angeles; San Francisco; and Washington, DC), enrolling 2,628 women. The cohort was expanded during 2001–2002 to recruit younger women with limited disease progression [12]. Written informed consent was obtained after local human subjects committee approval. Follow-up continues, but this analysis includes information collected on adolescents aged 16–20 years who were followed for up to 3 years after enrollment.

Participating women had medical, social, and sexual histories taken by trained interviewers every 6 months, with physical examination and conventional cervical cytology. Pap smears were interpreted centrally (Dianon, New York, NY [formerly Kyto or Kyto Meridien]) using the Bethesda System for cervicovaginal cytological diagnosis [13]. For this study, HAART was defined as any use of highly active antiretroviral therapy at or after cervical disease treatment; definitions of HAART followed those in DHHS/Kaiser guidelines [14].

Colposcopy was recommended for all grades of epithelial abnormality, including atypical squamous cells. Cervical disease treatment decisions were not specified by study protocols. Cytological, colposcopic, and histological findings were entered into a central database. Biopsy slides were not centrally reviewed. Prevalence and incidence were determined. Women were eligible for prevalence analysis if they were 20 years or younger at enrollment. Women were eligible for incidence analysis if they had at least 1 follow-up cytology result.

Reported demographic variables from the baseline visit included age, ethnicity, marital status, use of alcohol, number of male sex partners, lifetime number of male sex partners, HIV risk category, history of trading sex for money or drugs, parity, and HPV present and type. For HIV-seropositive women, CD4 count, HIV viral load, and HAART use were also assessed at baseline.

Demographics were compared by HIV status using Fisher exact test or the χ^2 test for categorical variables and Student *t* test or Wilcoxon 2-sample test for continuous variables. The outcome of interest was high-grade cervical disease, defined as either grade 2 or 3 cervical intraepithelial neoplasia (CIN) on biopsy or HSIL on cytology. The prevalence of high-grade cervical disease was calculated as the number of cases divided by the number of adolescents at enrollment. The cumulative incidence of high-grade cervical disease was calculated as the number of cases divided by the total number of adolescents eligible for follow-up. Incidence density was calculated as the number of cases divided by the total person time during follow-up. Relative risk and 95% CIs were calculated for determining the risk of high-grade cervical disease by HIV status. All analyses were conducted using SAS software version 8.2 (SAS Institute, Cary, NC).

RESULTS

Demographic and medical characteristics of the 132 enrollees (45 HIV seropositive and 87 seronegative) younger than the age of 21 with baseline results are given in Table 1. The median age was 19.9 years among HIV-seropositive women and 19.5 years among HIV-seronegative women ($p = .18$). HIV-seropositive women were more likely than seronegative women to have been married and to have been pregnant but less likely to have used alcohol. The HIV-seropositive women had fewer sexual partners in the 6 months before enrollment (mean, 1.5 for seropositive women vs 2.1 for seronegative women; $p = .03$ by Wilcoxon 2-sample test) but not over a lifetime (mean, 11.4 vs 13.8; $p = .16$). They also were more likely to have heterosexual risk factors for HIV transmission. The median CD4 lymphocyte count among women with HIV was 437 cells/mm³, and the median HIV ribonucleic acid level was 4,000 copies/mm³. Only 8 (18%) of the 45 HIV-seropositive women were using HAART at baseline.

At enrollment, none of the participants had high-grade cervical disease, defined as HSIL or CIN 2,3, and none had glandular abnormalities. For the incidence analysis, 9 women were excluded because follow-up cytology was not available (1 HIV seropositive and 8 HIV seronegative), leaving 123 adolescents (44 HIV seropositive and 79 seronegative) with up to 3 years of observation (median follow-up, 2.6 years for both HIV-seropositive and HIV-seronegative women).

HIV-seropositive women were more likely to have prevalent abnormal cytology of any grade (24 [53%] HIV-seropositive women vs 26 [30%] HIV-seronegative women; $p = .01$). There were no differences in the prevalence of ASCUS results (13 [29%] in HIV-seropositive women vs 21 [24%] in seronegative women; $p = .67$), but LSIL were more common in HIV-seropositive women (11 [24%] vs 5 [6%]; $p = .004$).

During follow-up, only 8 women developed HSIL or CIN 2,3; 5 were HIV seropositive, and 3 were seronegative. Six of these had at least 1 previous abnormal cytology result. None developed invasive cancer. Among women with HIV, incident high-grade cervical disease was not more common in women with abnormal Pap results at baseline (1 [4%] of 24 women with baseline cytological abnormalities vs 4 [20%] of 20 with negative baseline Pap; $p = .10$). The 8 incident abnormalities included 5 with CIN 2 on biopsy (2 HIV seropositive and 3 HIV seronegative), 2 with HSIL cytology subcategorized as moderate dysplasia but not confirmed histologically (both HIV seropositive), and only 1 with CIN 3 (HIV seropositive). The 1 woman with CIN 3 had a baseline CD4 count of 774 and an HIV viral load of 1,200,000 copies/mm³. Cumulatively, HSIL or CIN 2,3 developed in 6.5% of women over the 3 years of observation after enrollment (11% of HIV-seropositive women and 4% of HIV-seronegative women; $p = .13$ [Fisher exact test]). This represented an incidence rate for HSIL/CIN 2,3 of 2.7/100 person-years (4.8/100 person-years in HIV-seropositive women and 1.6/100 person-years in HIV-seronegative women; relative risk = 3.1; 95% CI = 0.76–12.74; $p = .13$ [Fisher exact test]).

DISCUSSION

Although women with HIV are at increased risk for CIN, we have previously shown that their risk for high-grade cervical disease is relatively low over prolonged follow-up, although it remains higher than that for HIV-seronegative women [2]. Previous work with adolescents suggested that the risk of HSIL cytology is approximately 4-fold higher among those with HIV [10]. Our results using a combination of cytology and colposcopic biopsy are confirmatory, although our risk estimate was lower and the difference in risk according to serostatus did not reach statistical significance. We also found that most cases of high-grade cervical disease were preceded by ASCUS or LSIL cytology. In both studies, the annual incidence of high-grade cervical disease was less than 10%. Neither study reported an incident cancer. Taken together, these findings suggest that young HIV-infected women with borderline cytological abnormalities can be followed rather than prophylactically treated without risk of missed cancer.

Current guidelines suggest annual cytology for adolescents with ASCUS or LSIL [9]. The increased risk of high-grade cervical disease in this study and the REACH study suggests

that colposcopy is indicated for the evaluation of borderline abnormalities in HIV-infected adolescents for 2 reasons. On the one hand, colposcopy will identify women with CIN 3 who need treatment. On the other hand, only 1 of 5 HIV-seropositive women with high-grade cervical disease in this study had CIN 3. Although numbers are small, colposcopy and biopsy may be important for distinguishing adolescents with CIN 3, a recognized cancer precursor, from those with CIN 2, which may reflect a transient HPV infection. In addition, a proportion of women with HSIL cytology have CIN 1 or no lesion colposcopically. For these reasons, cytology studies may overestimate the risk of cancer, and it may be possible to follow some of these young women with serial colposcopy and cytology to avoid the morbidity of treatment.

In both this study and the REACH study, cytology was performed at 6-month intervals. Whether semiannual cytology is needed to identify high-grade cervical disease or results in overdiagnosis of lesions that would resolve between annual tests remains to be determined. Surveillance colposcopy does not seem to be required, however. As in older women, the transition time between infection by an oncogenic HPV and the actual development of CIN 3 in adolescents seems to occur over sufficient time to allow serial cytology to identify disease before cancer develops.

Human papillomavirus is very common among young women, and HPV prevalence is even higher in adolescents with HIV [10]. Human papillomavirus infection causes viral cytopathic effects that may mimic HSIL cytologically. In young immunocompetent women, the majority of such intermediate lesions will regress [15]. Cervical disease treatment is associated with an increased risk of preterm delivery and other pregnancy complications [16]. Minimizing intervention for what is likely to be a transient or nonprogressive HPV infection may reduce the risk of future pregnancy problems. For young women with HIV, our results indicate that rapid progression to high-grade cervical disease is unlikely, and observation with cytology and colposcopy in line with current guidelines for HIV-uninfected women is unlikely to result in missed cancers.

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Table 1Baseline Characteristics of Adolescents With and Without HIV (*n* = 132)

Characteristic	Seropositive (<i>n</i> = 45)	Seronegative (<i>n</i> = 87)	<i>p</i> ^a
Age, y			
16–18	10 (22.2)	24 (27.6)	0.60 ^b
19	15 (33.3)	32 (36.8)	
20	20 (44.4)	31 (35.6)	
Mean (median)	19.7 (19.9)	19.5 (19.5)	0.26 ^c , 0.18 ^d
Ethnicity			
Black non-Hispanic	22 (48.9)	41 (47.1)	0.40 ^b
Hispanic	17 (37.8)	40 (46.0)	
White non-Hispanic/other	6 (13.3)	6 (6.9)	
Ever married			
Yes	21 (46.7)	24 (27.6)	0.03
No	24 (53.3)	63 (72.4)	
Smoking status			
Never smoked	28 (62.2)	44 (50.6)	0.43 ^b
Former smoker	5 (11.1)	11 (12.6)	
Current smoker	12 (26.7)	32 (36.8)	
Alcohol use			
Use	18 (40.0)	51 (58.6)	0.02
Abstain	27 (60.0)	36 (41.4)	
No. male sexual partners in previous 6 mo			
None	6 (13.3)	6 (6.9)	0.09 ^b
1 partner	28 (62.2)	44 (50.6)	
2 or more partners	11 (24.4)	37 (42.5)	
Lifetime male sex partners			
1–2	12 (26.7)	11 (12.6)	0.23 ^b
3–5	12 (26.7)	25 (28.7)	
6–10	9 (20.0)	24 (27.6)	
11+	12 (26.7)	27 (31.0)	
Risk category			
Heterosexual	23 (51.1)	7 (8.1)	<0.0001
Intravenous drug/transfusion	1 (2.2)	5 (5.8)	1.00
No identified risk	21 (46.7)	75 (86.2)	Reference
Traded sex for money/drugs			
Yes	4 (8.9)	6 (6.9)	0.73
No	41 (91.1)	81 (93.1)	
Currently pregnant			
Yes	5 (11.1)	5 (5.8)	0.31
No	40 (88.9)	82 (94.3)	

Characteristic	Seropositive (<i>n</i> = 45)	Seronegative (<i>n</i> = 87)	<i>p</i> ^{<i>a</i>}
Ever been pregnant			
Yes	40 (88.9)	53 (60.9)	0.001
No	5 (11.1)	34 (39.1)	
CD4 count, cells/mm ³			
<200	4 (8.9)	NA	
200–500	23 (51.1)		
501+	18 (40.0)		
Viral load, copies/mm ³			
<4,000	18 (40.0)	NA	
4,000+	27 (60.0)		
HAART use at baseline			
Yes	8 (17.8)	NA	
No	37 (82.2)		

Data are presented as frequency (%).

NA, not applicable; HAART, highly active antiretroviral therapy.

^{*a*}Fisher exact test *p* value unless otherwise specified.

^{*b*}By χ^2 test.

^{*c*}By Wilcoxon 2-sample test.

^{*d*}NA.