ARTICLE

Prevalence of and Risks for Cervical Human Papillomavirus Infection and Squamous Intraepithelial Lesions in Adolescent Girls

Impact of Infection With Human Immunodeficiency Virus

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Context: Data suggest that in adults, human papillomavirus (HPV) infections and their sequalae, squamous intraepithelial lesions (SILs), occur more commonly among human immunodeficiency (HIV)–infected women because of the HIV-associated CD4+ T-cell immunosuppression. Since adolescents are more likely to be early in the course of HIV and HPV infections, the study of both infections in this age group may help elucidate their initial relationship.

Objective: To examine the prevalence of and risks for cervical HPV infection and SILs by HIV status in a population of adolescent girls.

Participants: Subjects recruited at each of the 16 different US sites participating in a national study of HIV infection in adolescents.

Main Outcome Measures: Cervical HPV DNA findings using polymerase chain reaction detection techniques and Papanicolaou smear from baseline visits. Infection with HPV was categorized into low- (rarely associated with cancer) and high- (commonly associated with cancers) risk types.

Results: Of 133 HIV-infected girls, 103 (77.4%) compared with 30 (54.5%) of 55 noninfected girls were positive for HPV (relative risk [RR], 1.4; 95% confidence interval [CI], 1.1-1.8). The risk was for high-risk (RR, 1.8; 95% CI, 1.2-2.7) but not low-risk (RR, 1.2; 95% CI, 0.4-3.9) HPV types. Among the girls with HPV infection, 21 (70.0%) of the non–HIV-infected girls had normal cytologic findings compared with only 29 (29.9%) of the HIV-infected girls ($P<.001$). Multivariate analysis showed that HIV status was a significant risk for HPV infection (odds ratio [OR], 3.3; 95% CI, 1.6-6.7) and SIL (OR, 4.7; 95% CI, 1.8-14.8), but CD4 cell count and viral load were not associated with infection or squamous intraepithelial lesions. Only 9 girls had a CD4+ T-cell count of less than 0.2 cell $\times$ 10^9/L.

Conclusions: High prevalence of HPV infection in both groups underscores the risky sexual behavior in this adolescent cohort. Rates of HPV infection and SILs were higher among HIV-infected girls, despite similar sexual risk behaviors and the relatively healthy state of our HIV-infected group. Infection with HIV may enhance HPV proliferation through mechanisms other than CD4 immunosuppression, particularly early in the course of HIV infection.

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Editor's Note: If you'd like an example of double jeopardy in an adolescent population, read this study.

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THE IMPORTANCE of human papillomavirus (HPV) as a necessary but insufficient component in the development of squamous cell cervical cancers has been well established. Numerous cofactors have been examined to help explain the imbalance between the very high prevalence of HPV infection and the relatively low incidence of anogenital cancers in the United States.[1,2] The high prevalence of HPV-associated squamous intraepithelial lesions (SILs) in human immunodeficiency virus (HIV)–infected individuals has suggested that the host immune response may play a significant role in the development of HPV-associated cancers.[3,4] The higher rates of HPV and SILs in HIV-infected women are thought to be attributed specifically to T-cell paucity and dysfunction.[3-7] However, a few studies have not found a correlation between SILs or HPV DNA detection and CD4+ T-cell

SUBJECTS, MATERIALS, AND METHODS

SUBJECT POPULATION

We report on data collected from March 1, 1996, through December 31, 1997, as part of an ongoing cohort study of HIV infection in adolescents, ie, the Reaching for Excellence in Adolescent Care and Health (REACH) Project of the Adolescent Medicine HIV and AIDS [Acquired Immunodeficiency Syndrome] Research Network. The description of the cohort, recruitment, follow-up, and consent procedures are given in detail elsewhere.[9] Briefly, subjects included adolescent girls aged 13 to 18 years known to be seropositive for HIV and in health care. The REACH study involves 16 different clinical sites in 13 US cities. All subjects consented to participate in this study according to the guidelines of their respective institutions.[9] The cohort study only includes adolescents who by history have acquired HIV through sexual activity or intravenous drug use. The study also recruits girls of comparable age with behaviors that put them at risk for HIV infection, who are seronegative for HIV infection. Information on demographics and contraceptive use was obtained during a face-to-face interview. Information on sensitive sexual behaviors was collected using a confidential interactive computer interview designed specifically for the REACH study.[9]

Gynecologic examination for all subjects at the initial study visit included, in the following order: vaginal samples for evidence of bacterial vaginosis, cervical lavage with 10 mL of isotonic sodium chloride solution for HPV testing, an endocervical and exocervical sample for cytologic examination, and an endocervical sample for *C trachomatis* and *N gonorrhoeae* testing. Vaginal samples were tested for pH and positive results of a "whiff" test using potassium hydroxide, and were examined for the presence of clue cells on isotonic sodium chloride solution wet mounts. Bacterial vaginosis was diagnosed using the Amsel criteria.[10]

Cytologic smears were fixed immediately using a spray preservative and sent to a centralized laboratory at the University of California, San Francisco, for review. Diagnoses of atypical cells of undetermined significance (ASCUS), low-grade SILs (LSILs), and high-grade SILs (HSILs) were made according to the Bethesda system for rating cytologic specimens.[11]

Samples for *C trachomatis* and *N gonorrhoeae* testing were placed in transport media and refrigerated or placed on ice for no more than 4 hours before freezing at −70°C until processing. Samples were sent to a centralized laboratory for processing using the amplification-based ligase chain reaction technique (LCX STD system; Abbott Laboratories, Abbott Park, Ill).

HPV DNA TESTING

Cervical lavage samples were kept at room temperature no longer than 4 hours, and then stored at −70°C until processed at the centralized laboratory using polymerase chain reaction amplification technique as described previously.[12] Briefly, 40 µL of settled cellular material from 1-mL aliquots was removed and added to a digestion solution of proteinase K, Tris, EDTA, and laureth 12 for 2 hours at 55°C. The samples were then heated to 95°C for 10 minutes and stored at −20°C until the amplification process was begun. Two microliters of this thawed solution was added to a solution containing the primers as previously described.[12] Each solution contained consensus primers from the HPV late region 1 (L1) region (MY09/MY11) as well as primers for the amplification of β-hemoglobin as a positive control for the presence of cellular material and the integrity of the amplification reaction. To control for possible contamination, negative controls for each experiment included the amplification mixture containing all the above components except for target DNA, water controls, and non–HPV-infected cellular material (cell line C33-A). The amplified product was assayed using dot-blot analysis for the presence of a positive β-hemoglobin signal (the internal positive control), a generic probe mix that identified approximately 25 different HPV types, and specific HPV types including HPV 6, 11, 42, and 44 (low cancer risk types), and 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, and 58 (high cancer risk types). Polymerase chain reaction

count.[8] These differences may be attributable to a disparity in the stages of the natural history of HPV or HIV infection in the various study populations. Most HPV studies have been performed in women with relatively long periods of sexual activity and histories of promiscuity who were seropositive for HIV and who may reflect the later stages of the natural history of HPV infections.[2,5,6] Studies of adolescents represent a unique opportunity to examine HPV infections in HIV-infected individuals with a more limited history of sexual activity and relatively recent HIV and HPV infections.

Our initial purpose was to examine the prevalence of HPV infection and SILs of the cervix in HIV-infected adolescents compared with noninfected adolescents with similar high-risk behaviors. Second, we examined the association between specific risk factors for HPV infection and SILs, including level of immunosuppression defined by $CD4^+$ T-cell count and viral load, sexual behavior, substance use, hormonal influences, tobacco use, and coinfections of the genital tract (including *Chlamydia trachomatis, Neisseria gonorrhoeae,* and bacterial vaginosis).

RESULTS

One hundred ninety-seven adolescent girls had samples obtained for HPV testing at the baseline visit. Comparisons for demographic and behavioral characteristics of the 138 HIV-infected and 59 noninfected girls are described in **Table 1**. Most of our HIV-infected subjects were relatively healthy, with high $CD4^+$ T-cell counts and relatively low HIV viral loads. The immunological and virological profiles and current antiretroviral therapy status of the HIV-infected girls are described in **Table 2**.

HPV DNA RESULTS

Nine girls had inadequate samples (negative for β-hemoglobin) for HPV analysis. Of the remaining samples

data were classified as negative, positive for the specific types identified, or positive with type unknown if the sample showed a positive result with the generic probe but did not hybridize to any of the aforementioned specific probes. Samples negative for β-hemoglobin were excluded from analysis. For analysis, HPV was defined by the presence of any HPV (positive using results of generic probe), high-risk HPV type only, low-risk HPV type positive only, and HPV type unknown. The high-risk HPV types were further categorized using the following phylogenetic DNA patterns: HPV-16–like grouping included types 16, 31, 33, 35, 52, and 58; HPV-18–like grouping included types 18, 39, and 45; and intermediate-risk grouping included types 51 and 56.[13]

Quantitative immunophenotyping of T cells for the CD4 marker was performed at the individual clinical sites in certified laboratories using standardized AIDS Clinical Trials Group protocols.

The HIV plasma viral loads were tested at a centralized laboratory using nucleic acid sequence base amplification (NASBA; Organon Technika, Rockville, Md). The assay performed used 200 µL of plasma, resulting in a lower limit of detection of 400 copies/mL of plasma.

DATA ANALYSIS

The statistical test used to evaluate 4-fold contingency table comparisons for statistical significance was the χ^2 corrected for continuity. Where appropriate, the Fisher exact test was used. Comparisons of subgroups within larger contingency tables were undertaken only when the χ^2 test for the larger table was significant at the level of $P<.01$.[14] Techniques to adjust for multiple comparisons were not used in the initial analyses to avoid missing the chance of observing clinically important associations.[15] Relative risk (RR) was computed as the ratio of the rate of an outcome (HPV or SIL) in a group of subjects with a risk factor to the rate of the outcome in a group of subjects without the risk factor. The confidence intervals (CIs) for RR are given as in Katz et al,[16] based on large-sample approximation techniques, and their validity is good for moderate to large samples. For some of the smaller contingency tables presented, the CIs are crude approximations and may present apparently conflicting results such as a significant association associated with a CI for an RR including 1.[17,18]

Multivariate analyses for HPV and SILs were examined as outcomes in similar fashion. Both outcomes were considered to be dichotomous, with HPV as present or absent, regardless of HPV type; SILs as present or absent; with ASCUS considered to be absence of SILs. The first step in the analysis of each outcome was the assessment of the univariate contingency tables of the associations of risk factors thought to be biologically plausible predictors (data not shown). Contingency table analyses were pursued as above, providing a series of statistically significant and/or clinically important risk factors to be examined in multivariate analysis. The second step in the analysis was to examine simultaneously putative risk factors for each outcome as well as potential covariates (eg, age) using a binary logistic regression model.[19] The backward stepwise procedure was used for subjects who were seropositive and seronegative for HIV infection, separately and combined. The model reported was for the entire cohort. The importance of individual variables included in the prediction models was measured by statistical significance. The logistic SAS procedure (SAS Institute Inc, Cary, NC) provided several measures of association between the probabilities predicted by the model and the observed responses, of which the Goodman-Kruskal γ was used.

Risks factors for HPV infection and SIL included HIV status, age, race, presence of external genital warts, *C trachomatis, N gonorrhoeae,* history of ever smoking more than 100 cigarettes, current number of cigarettes smoked per day, type of hormonal contraceptive use (current and in the past 3 months), numbers of sexual partners in lifetime and the past 3 months, abstinence, unprotected last intercourse, sexual identity (bisexual vs heterosexual), frequency of current drug use, and, for SIL, HPV infection. Drug use included alcohol and other illicit drugs such as amphetamines and barbituates, but not marijuana, since these data were missing on approximately half the sample because of a problem in the computer program at the baseline visit. No intravenous drug use was reported in this cohort.

(n = 188), 133 (70.7%) were HPV infected. Of those with HPV, 10 (7.5%) had a low-risk HPV type only; 89 (66.9%), a high-risk HPV type; and 34 (25.6%), HPV type unknown only. Seropositive HIV status was a significant risk for HPV infection. However, the risk was primarily for high-risk rather than low-risk HPV types. **Table 3** describes the risk for high-risk, low-risk, and specific HPV type subgroups. There were no statistically significant differences between HIV status groups for those with more than a single HPV type. Of the 99 subjects with identified HPV types, 7 (35.0%) of the 20 non–HIV-infected girls had 2 or more HPV types compared with 38 (48.1%) of the 79 HIV-infected girls (χ^2_1, $P = .29$).

ASSOCIATION BETWEEN SIL AND HPV AND HIV STATUS

One hundred seventy-two girls had adequate cytologic specimens for comparison with HPV status. Eighty-eight (51.2%) had abnormal cytologic findings; of these, 38 (43.2%) had ASCUS, 44 (50.0%) had LSILs, and 6 (6.8%) had HSILs. Table 3 describes the risk for any HPV infections by cytologic status. Not unexpectedly, equivalently high proportions of SIL cases were associated with HPV infection in HIV-infected and noninfected girls. Infection with HPV was found in 40 (90.9%) of the HIV-infected girls with SILs and 6 (100%) of the non–HIV-infected girls with SILs ($P = .44$). In comparison, a higher proportion of girls with ASCUS had HPV infection in the HIV-infected than the non–HIV-infected girls. Twenty-eight (90.3%) of the HIV-infected girls with ASCUS were positive for HPV compared with 3 (42.9%) of the non–HIV-infected girls with ASCUS ($P = .01$). The proportion of girls with normal cytologic findings who had HPV infection was similar for HIV- and non–HIV-infected girls. Twenty-nine (61.7%) of the HIV-infected group compared with 21 (56.8%) of the non–HIV-infected group with normal cytologic findings had an HPV infection ($P = .65$).

Table 1. Demographics and Behavioral Characteristics of the Cohort*

Characteristic	HIV Seropositive	HIV Seronegative
Mean age (SD)	16.8 (1.2)†	16.3 (1.3)†
African American	104 (75.4)	40 (67.8)
Age of first consenting vaginal sex ≤12 y	28 (25.9)	9 (20.0)
No. of lifetime sexual partners		
0-4	42 (31.6)	23 (41.8)
5-10	47 (35.3)	20 (36.4)
>10	44 (33.1)	12 (21.8)
Last intercourse unprotected	48 (36.9)‡	30 (54.6)‡
Smokes ≥20 cigarettes/d	12 (9.2)	4 (7.8)
Currently receiving hormonal therapy	53 (38.7)	24 (40.7)
Currently pregnant	8 (5.8)	1 (1.8)
Chlamydia trachomatis and/or *Neisseria gonorrhoeae* infection	27 (19.7)	8 (14.0)
Bacterial vaginosis	19 (15.8)	8 (14.8)
Dropped out of school	35 (25.6)	8 (13.6)

*HIV indicates human immunodeficiency virus. Unless otherwise indicated, data are given as number (percentage) of subjects. Denominators vary owing to missing values.
†P≤.005.
‡P<.05.

Table 2. Therapy and Immunological and Virological Profiles of HIV-Infected Adolescent Girls*

Characteristic	No. (%) of Subjects
Viral load, copies of RNA/mL	
<400	25 (18.4)
400-10 000	67 (49.3)
>10 000-50 000	28 (20.6)
>50 000	16 (11.7)
CD4 cell count, $\times 10^9$/L	
>0.5	68 (50.0)
>0.2-0.5	59 (43.4)
≤0.2	9 (6.6)
Current antiretroviral therapy use	
None	86 (62.3)
Without protease inhibitor	36 (26.1)
With protease inhibitor	16 (11.6)

*Denominators may vary owing to missing data.

When we examined the rate of abnormal cytologic findings among girls infected with HPV, we found that HIV-infected girls were less likely to have a latent infection, defined as normal cytologic findings and positive results of the HPV test, than were non–HIV-infected girls (**Figure**) (χ^2_1 = 15.4; P<.001). Twenty-nine (29.9%) of the HIV-infected girls who had HPV also had normal cytologic findings compared with 21 (70.0%) of the non–HIV-infected girls with HPV (RR, 0.4; 95% CI, 0.3-0.6; P = .001). Among girls with high-risk HPV, 14 (20.3%) of the HIV-infected girls had normal cytologic findings compared with 11 (68.8%) of the non–HIV-infected girls (RR, 0.3; 95% CI, 0.2-0.5; P<.001). In each of the HIV groups, 1 (25%) of 4 girls with low-risk HPV type had normal cytologic findings; sample size was insufficient for any meaningful analysis.

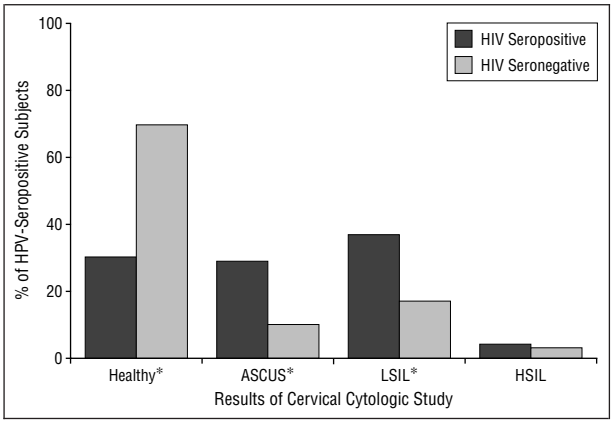
Table 3. Risk of HPV by Cytologic Studies and HIV Status[a]

HPV Type Outcome	HIV Status, No. of Subjects: Seropositive (n = 133)	Seronegative (n = 55)	Relative Risk (95% Confidence Interval)[b]	P[c]
No HPV infection	30	25	. . .	. . .
Any HPV	103	30	1.4 (1.1-1.8)	.002
High-risk HPV[d]	73	16	1.8 (1.2-2.7)	<.001
Low-risk HPV[e]	6	4	1.2 (0.4-3.9)	.75
HPV type unknown[f]	24	10	1.6 (0.8-2.8)	.18
HPV 16–like[g]	63	13	2.0 (1.2-3.1)	<.001
HPV 18–like[h]	22	3	3.9 (1.3-12.0)	<.001
HPV intermediate[i]	14	2	4.3 (1.1-17.5)	.02
Cytologic subgroups				
Benign[j]				
No HPV	18	16	. . .	. . .
Any HPV	29	21	1.1 (0.8-1.6)[g]	.65
ASCUS[k]				
No HPV	3	4	. . .	. . .
Any HPV	28	3	2.1 (0.9-5.0)[h]	.01
SILs[l]				
No HPV	4	0	. . .	. . .
Any HPV	40	6	0.9 (0.8-1.0)[i]	.45

[a]HPV indicates human papillomavirus; HIV, human immunodeficiency virus; ASCUS, atypical cells of undetermined significance; SILs, squamous intraepithelial lesions; and ellipses, reference group.
[b]Indicates relative risk for HPV infection. For comparisons of the risk of subtypes of HPV based on HIV status, subjects included in the 2 × 2 comparisons contingency tables were those with the specific subtype and those with no HPV.
[c]In our comparisons, the statistical test used for the P values was χ^2_1.
[d]Includes HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, and 58.
[e]Includes HPV types 6, 11, 42, and 44.
[f]Includes specimens with a positive reaction to a generic probe but negative for the specific HPV probes listed above.
[g]Includes HPV types 16, 31, 33, 35, 52, and 58.
[h]Includes HPV types 18, 39, and 45.
[i]Includes HPV types 51 and 56.
[j]Relative risk for any HPV among women with benign cytologic findings.
[k]Relative risk for any HPV among women with ASCUS.
[l]Relative risk for any HPV infection among women with SILs.

VIRAL LOAD, CD4+ T-CELL COUNT, HPV INFECTION, AND SIL FOR WOMEN WITH HIV INFECTION

Among women with HIV infection, no association was found between HIV viral load and HPV infection or CD4+ T-cell count and HPV infection. Eighty-one percent of the women with a viral load of 10 000 copies of RNA/mL or greater were found to be positive for HPV compared with 76.4% of the women with a viral load of less than 10 000 copies of RNA/mL (RR, 1.1; 95% CI, 0.9-1.3; P = .56). Eight (88.9%) of 9 girls with a CD4+ T-cell count of no more than 0.2 cell × 10^9/L were positive for HPV compared with 76.4% of 123 girls with a CD4+ T-cell count of greater than 0.2 cell × 10^9/L (RR, 1.2; 95% CI, 0.9-1.5; P = .68). In addition, even when using different cutoff values for CD4+ T-cell count (<0.5 cell × 10^9/L) and HIV viral load (less than detectable or categorical), no differences were found. Similarly, no significant associations were found between high HIV viral load (RR, 1.0; 95% CI, 0.7-1.3; P = .70) or low CD4+ T-cell count and high-risk HPV types (RR, 1.2; 95% CI, 0.9-1.8; P = .42).



Association between abnormal cervical cytologic findings and human immunodeficiency virus (HIV) status among human papillomavirus (HPV)–infected adolescent girls. Overall $\chi^2_3 = 15.7$, for difference among the cytologic categories, with P<.001. Asterisk indicates that the χ^2_1 statistic for the difference in rates of abnormal cytologic findings between HIV-infected and non–HIV-infected girls is greater than the tabled value of χ^2 at P = .05. ASCUS indicates atypical cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; and HSIL, high-grade SIL.

Table 4. Predicted Probability of SIL Based on Logistic Model*

Chlamydia	HIV	HPV	No. of Subjects	Predicted Probability (95% Confidence Interval)
–	+	+	86	0.49 (0.38-0.60)
+	+	+	16	0.24 (0.09-0.48)
–	–	+	24	0.17 (0.07-0.35)
–	+	–	26	0.14 (0.06-0.33)
+	–	+	5	0.06 (0.02-0.22)
+	+	–	4	0.05 (0.01-0.20)
–	–	–	22	0.03 (0.01-0.12)
+	–	–	0	. . .

**SIL indicates squamous intraepithelial lesion; HIV, human immunodeficiency virus; HPV, human papillomavirus; minus sign, negative; plus sign, positive; and ellipses, not applicable. The logistic equation for predicting SIL is probability (SIL) = 1/{1 + Exp[– (–3.33 + 1.55 × HIV + 1.73 × HPV infection – 1.13 × chlamydia infection)]}.*

No associations were found between viral load or CD4+ T-cell count and SIL. Twelve (31.6%) of 38 girls with a viral load of 10 000 copies of RNA/mL or greater had SILs, compared with 32 (39.5%) of 81 girls with a viral load of less than 10 000 copies of RNA/mL (RR, 0.8; 95% CI, 0.5-1.4; $P = .40$). Forty-one (36.9%) of the 111 girls with a CD4+ T-cell count of greater than 0.2 cell × 10^9/L had SILs, compared with 3 (33.3%) of the 9 girls who had CD4+ T-cell counts of less than or equal to 0.2 cell × 10^9/L (RR, 0.9; 95% CI, 0.4-2.3; $P = .99$). No differences were found again when using different cutoff values for CD4+ T-cell counts (<0.5 cell × 10^9/L) and HIV viral load (less than detectable vs detectable).

RISKS FOR HPV INFECTION AND SILs

The risk factors with P values indicating a low likelihood of chance association were selected for the logistic models using backward stepwise regression. These included HIV status ($P<.001$) and smoking at least 20 cigarettes per day in the past 3 months ($P = .002$) for HPV infection, and HIV status ($P = .003$), HPV infection ($P = .003$), and chlamydia infections ($P = .06$) for SILs. Logistic regression analysis performed for HIV-infected girls only found no significant statistical associations between CD4+ T-cell count, viral load, or current antiretroviral therapy and HPV or SILs.

The quality of the models in predicting the outcomes of HPV and SILs was modest using the criterion of the Goodman-Kruskal γ (maximum value, 1). For HPV, γ = 0.6; for SILs, γ = 0.7. The logistic regression equation for predicting HPV is as follows:

$$\text{Probability (HPV)} = 1/\{1 + \text{Exp}[-(0.27 + 1.19 \times \text{HIV} - 1.72 \times \text{Smoker})]\},$$

where Exp indicates the mathematical constant e raised to the power shown.

For HPV, the odds ratio (OR) for HIV status was 3.3 (95% CI, 1.6-6.7); for smoking at least 20 cigarettes per day in the last 3 months, 0.2 (95% CI, 0.06-0.5). The predicted probability of HPV based on the logistic model showed the highest probability of 0.8 (95% CI, 0.7-0.9) if HIV serostatus was positive and less than 20 cigarettes were smoked per day in the past 3 months. In comparison, the lowest probability, 0.2 (95% CI, 0.07-0.4), was found if HIV serostatus was negative and at least 20 cigarettes per day were smoked.

The logistic regression equation for predicting SILs is as follows:

$$\text{Probability (SIL)} = 1/\{1 + \text{Exp}[-(-3.33 + 1.55 \times \text{HIV} + 1.73 \times \text{HPV Infection} - 1.13 \times \text{Chlamydia Infection})]\}$$

For SILs, the ORs for HIV status and HPV infection were 4.7 (95% CI, 1.8-14.8) and 5.6 (95% CI, 2.0-20.1), respectively. Chlamydia infection was found to be protective, with an OR of 0.3 (95% CI, 0.09-1.0). **Table 4** summarizes the predicted probability of SILs based on the logistic model for the various combinations of outcomes for HIV serostatus, HPV, and chlamydia infection status. Exclusion of the marginally statistically significant chlamydia infection from the model left HIV and HPV infection as remaining predictors, with trivial changes in their factor estimates or statistical significance.

COMMENT

We found that HPV is highly prevalent in HIV-infected and -noninfected adolescent girls. This high prevalence and the relatively high rate of other sexually transmitted infections most likely reflect the risky sexual behavior of both groups in our cohort.[1,20] The higher rate of HPV infection in the HIV-infected girls is similar to that in studies of adult women.[3-6,21] The recent study reported by Sun et al[3] found that the HPV prevalence among HIV-infected women was 56% compared with 31% among the non–HIV-infected women. This disparity was true for low- and high-risk HPV types in their study, and these differences were augmented by a decreasing CD4+ T-cell count. In contrast, the difference between the serostatus groups for prevalence of HPV in our study was found for the high-risk HPV types only, and no association was found for CD4+ T-cell count or viral load.

The higher prevalence rate of high- vs low-risk HPV types in both groups may be, in part, explained by the tendency of these high-risk types to persist more commonly than the low-risk HPV types.[12,22] In a previous study, 30% of nonimmunocompromised adolescent girls who were positive for a high-risk HPV type had a persistent HPV infection for 24 months compared with less than 10% who were positive for a low-risk HPV type.[12] Persistence of HPV also appears to be influenced by HIV status. Two recent studies have shown that HIV-infected women are at higher risk for HPV persistence than the non–HIV-infected women.[3,8] This association was found to be true at all CD4 strata, but was also enhanced by a decreasing $CD4^+$ T-cell count.

THE LACK OF association with $CD4^+$ T-cell count in our group was somewhat surprising. Although few subjects had a $CD4^+$ T-cell count of less than or equal to 0.2 cell $\times 10^9$/L, making any conclusions in this group difficult, 50.0% had $CD4^+$ T-cell counts of less than or equal to 0.5×10^9/L. Our logistic regression model also showed that other risk factors, including level of immunosuppression, risk behaviors, and current antiretroviral therapy, did not influence prevalence of HPV infection in the HIV-infected group. This observation is not unique to our cohort in that Vernon et al[8] and Langley et al[23] also found no association between $CD4^+$ T-cell count and the prevalence of HPV in their studies. Thus, impaired immune function may not explain entirely the disparity in HPV prevalence between girls with and without HIV infection. Infection with HIV has been shown to modulate cytokine expression, and it is plausible that HIV in cells of the cervical and vaginal epithelium may alter local cytokine expression such that HPV regulation is affected.[24,25] Infection with HIV has also been shown to up-regulate HPV expression through the HIV *TAT* gene in in vitro studies.[26]

Lack of association with low-risk HPV type and HIV status in our cohort is in contrast to most studies in women. First, our overall prevalence of low-risk HPV types only was much lower than that found in most adult populations. Since the absolute number of low-risk HPV types is small, statements concerning lack of differences between the serostatus groups cannot be conclusive. On the other hand, these differences seen between adolescents and adults may result from the vulnerability related to the time course of HIV infection in the population studied. It is possible that during the early course of HIV infection, only certain more aggressive HPV types are likely to persist or cause infection, whereas with more prolonged HIV disease, the vulnerability exists to all HPV types. This HIV-infected adolescent cohort is more likely to be early in their HIV disease process, based on their recent onset of intercourse (first possible exposure) and their relatively healthy clinical status. Age itself is unlikely to explain the disparity between our younger and other older cohorts, since the lower rate of low-risk HPV types compared with high-risk HPV types has been well described for adolescents and women.[1,14,27] The lack of association with sexual risk behavior in both groups is most likely a reflection of the high-risk behavior of the cohort in general as well as a reflection of high-risk partner behavior, which traditionally is important but difficult to capture.[22] The protective effect found for cigarette smoking was also reported by Ho et al.[22]

The association between SILs or HPV and cytologic findings was also found to be similar to that of most adult studies.[4-6] Non–HIV-infected women with HPV were more likely to have latent infection, whereas HIV-infected women with HPV were more likely to have abnormal cytologic findings. However, contrary to most adult studies,[3-5] $CD4^+$ T-cell counts and viral load did not help explain the association between HIV and SILs in our cohort. The link to SILs in HIV-infected girls underscores the possible interactions that may transpire between HIV and HPV, including the association between HIV and HPV persistence. Persistence of HPV has been linked closely to the development of SILs in several studies.[12,16,28]

Consistent with literature in nonimmunosuppressed adolescents,[29] most SILs identified in our study were LSILs. Since an LSIL is a reflection of active HPV proliferation and protein transcription,[30-32] HIV infection may enhance active HPV proliferation and protein transcription, even early in the course of HIV infection through interactions as discussed above, independent from but not exclusive of CD4 immunosuppression. Although the inverse relationship between chlamydia infection and SILs was observed with a modest *P* value and may reflect a chance association, 2 explanations can be considered. First, chlamydia infections may have resulted in an increased false-negative rate of the cytologic smears due to obscuring white blood cells.[33] Not surprisingly, 22 (81%) of the 27 subjects with chlamydia infections (data not shown) had inflammatory changes.[34] This association supports the notion that benign cytologic diagnosis in the face of chlamydia infections should be interpreted with caution. Second, clearance of chlamydia infections in mice is mediated by interferon-γ, and $CD4^+$ T-cells alone can confer protection.[35,36] If a similar mechanism is active in the genital tract of women infected with chlamydia, the local concentration of interferon-γ, a potent antiviral factor, may affect bystander cells infected with HPV and nonspecifically protect from the development of an SIL.[37] The relatively small number of subjects in additional subgroups prevented further investigations.

The difference in prevalence of HPV among girls with ASCUS by HIV serostatus reflects the ability of HPV to induce cytologic changes in the HIV-infected girls. Although only a small number of the non–HIV-infected girls received a diagnosis of ASCUS, the prevalence of HPV in this group with ASCUS was quite similar to that in the literature.[32] Approximately 40% of cytologic smears diagnosed with ASCUS were HPV positive in the non–HIV-infected group (a rate no different from that in the adolescents with normal cytologic findings), whereas 90.3% of the HIV-infected girls with ASCUS had HPV. This suggests that ASCUS in HIV-infected adolescents is most likely HPV induced. Prospective studies of the ASCUS and LSIL lesions are necessary to define important triage strategies for these diagnoses and cost-effectiveness of identifying and treating SILs in their early stages.

Certainly, the insensitivity of a single cytologic smear has been well described. Because our study used cyto-

logic studies as its criterion for SILs, we may have underdiagnosed the prevalence of SILs and, consequently, missed important risk factors associated with its development. To increase the sensitivity of cytologic smears on a cross-sectional study would have required the addition of routine screening colposcopy and biopsy. This most likely would have resulted in overaggressive diagnostic procedures as well as deterred study participation. The follow-up in anticipated longitudinal studies on this cohort with repeated cytologic studies will help us discriminate those with the single-point false-negative cytologic findings. In comparison, the lack of histological verification of SILs may have had an impact on our specificity as well. However, since more than 90% of the SILs were associated with HPV detection, and since we did not attempt to discriminate between LSILs and HSILs, we believe that use of cytologic studies to measure SILs did not alter our specificity-related conclusions.

There is a lack of prospective data on the natural history of HPV in HIV-infected adolescents. Much of the information has been extrapolated from cervical SIL studies in HIV-infected women, which suggests that HPV is an increasingly important cause of morbidity in HIV-infected individuals. However, the relevance of the adult literature to adolescents is limited, since physiological and behavioral characteristics of adolescents who acquire HIV are different from those of adults who acquire HIV. One of the highest-risk groups among nonimmunocompromised individuals for HPV infection are adolescents. Adolescents may have biological differences, such as cervical squamous metaplasia, that may increase their vulnerability to the development of persistent infection and/or disease. In addition, the study of HPV in the REACH cohort is unique, since most of the adolescents are early in their HIV course, allowing us to study HIV-HPV interaction before evidence of major immunosuppression.

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