ARTICLE

Association of Condom Use, Sexual Behaviors, and Sexually Transmitted Infections With the Duration of Genital Human Papillomavirus Infection Among Adolescent Women

Marcia L. Shew, MD, MPH; J. Dennis Fortenberry, MD, MS; Wanzhu Tu, PhD; Beth E. Juliar, MA, MS; Byron E. Batteiger, MD; Brahim Qadadri, BS; Darron R. Brown, MD

Objective: To examine the association of potentially modifiable factors such as condom use, sexual behaviors, and concurrent sexually transmitted infections with duration of genital human papillomavirus (HPV) infections among adolescent women.

Design: Longitudinal observational study.

Setting: Study conducted at 3 inner-city clinics in Indianapolis, Ind.

Participants: Forty-nine HPV-positive adolescents were tested frequently for HPV infection and provided sexual behavior diaries.

Main Exposures: Condom use, sexual behaviors, number of partners, and concurrent infections with *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis*.

Main Outcome Measures: Time from onset to clearance of type-specific HPV infections was analyzed with proportional hazard models. Adjusted hazard ratios (AHRs) were used to assess the effects of risk factors on the duration of HPV infection. Because viral clearance is a preferred outcome, a variable with an AHR less than 1 was considered a risk factor (ie, associated with reduced chance of viral clearance and prolonged infection).

Results: Prolonged HPV infection was associated with oncogenic HPV types (AHR, 0.58 [95% confidence interval (CI), 0.39-0.84]) less than median level of condom use during an HPV infection (AHR, 0.53 [95% CI, 0.33-0.84]) and coinfection with *C trachomatis* (AHR, 0.58 [95% CI, 0.31-0.89]) or *T vaginalis* (AHR, 0.32 [95% CI, 0.16-0.64]). Not having multiple sexual partners during an HPV infection was associated with early HPV clearance (AHR, 5.52 [95% CI, 3.28-9.30]).

Conclusions: These findings support public health messages of reducing the number of sexual partners, promoting routine condom use, and frequent sexually transmitted infection screening that may be beneficial with HPV infections.

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Author Affiliations: Division of Adolescent Medicine, Department of Pediatrics (Drs Shew and Fortenberry), Divisions of Biostatistics (Dr Tu and Ms Juliar) and Infectious Diseases (Drs Batteiger and Brown and Mr Qadadri), Department of Medicine, Department of Microbiology and Immunology (Drs Batteiger and Brown), and Regenstrief Institute (Dr Tu), Indiana University School of Medicine, Indianapolis.

THE PATHOGENESIS OF NEOplasia due to human papillomaviruses (HPVs) is a complex interaction of virus and host, with the ultimate incorporation of HPV DNA into the host cell genome, disruption of normal cell cycles, genomic instability, and initiation of abnormal cell clones.[1] Natural history studies show that 60% to 80% of HPV infections become undetectable over an 8- to 10-month period.[2-4] However, prolonged infection (commonly termed *HPV persistence*) appears to be a necessary but not sufficient link from initial HPV infection to subsequent neoplasia.[5,6]

Factors associated with longer HPV infections are not well defined, especially for adolescents. Infection by oncogenic viral types (ie, the approximately 20 viral types frequently identified in cancer tissue) is associated with longer HPV infection duration.[5,7,8] Other associated factors associated with longer-duration infections include older age, multiple sex partners, cigarette smoking,[9-12] immune suppression,[13] and hormonal contraception.[14] Recent studies linking genital *Chlamydia trachomatis* infections to cervical neoplasia suggest a potential role for concurrent infection in the duration of HPV infection.[15-17] Many of these earlier studies are limited by relatively infrequent follow-up intervals (ie, at 3- to 6-month intervals), inadequate assessment of concurrent sexually transmitted infections (STIs) and sexual and contraceptive behaviors, and exclusion of younger sexually active women. Given the high prevalence of sexually transmitted HPV infection among young women, additional research is needed to better define poten-

tially modifiable factors associated with HPV persistence.

The goal of this study was to assess factors associated with the duration of HPV persistence among a cohort of middle- and late-adolescent women. Relatively shorter sampling intervals, sensitive HPV diagnostic tests, assessment of concurrent STI, and detailed measures of sexual and contraceptive behavior were used to address limitations of previous research. Quarterly and weekly self-obtained vaginal specimens were used to follow the course of HPV infection. Self-obtained specimens are well accepted by young women and of comparable accuracy to clinician-obtained specimens.[18-20]

METHODS

STUDY DESIGN

A description of the methods and summary of the distribution of HPV types and natural history of infection in this sample is published elsewhere.[4] Briefly, women aged 14 to 17 years, attending 1 of 3 primary care adolescent health clinics, were enrolled in a 27-month observational study of biological and behavioral factors related to STI. Study enrollment began in the spring of 1999, and the last participant in this study sample completed the observation in 2002. All eligible women were identified by clinical schedules based on age criteria, and attempts were made to recruit all eligible women at that or a subsequent clinical visit. Each participant was recruited during clinic visits by study personnel who obtained the participant's informed consent and parental permission. Prior sexual experience was not an entry criterion. No information was obtained on those who refused participation, but all eligible women were recruited equally and demographic and STI data of the cohort mirrored that of the clinic population. None of the participants had known immunodeficiency conditions at enrollment or during the follow-up period. Data analyses were limited subsequently to the 49 subjects who were infected with HPV. The research was approved by the institutional review board of Indiana University/Purdue University at Indianapolis.

At enrollment, participants received a physical examination; provided clinician-obtained vaginal and cervical specimens for STI testing; and underwent a face-to-face interview. The cycle of clinical examination, STI testing, and interview was repeated at approximately 3-month intervals for 27 months. The enrollment interview, and subsequent quarterly interviews, provided detailed information about sexual behaviors, including condom use and hormonal contraceptive use. Participants received $20 for time and effort required for each interview.

In addition, all participants completed multiple periods of daily diary completion and weekly self-obtained vaginal specimens. Each diary completion period lasted approximately 84 days (12 weeks) and was initiated and ended by a clinic visit as described earlier. Each 12-week diary collection period was followed by a 12-week rest period in which no diaries or vaginal specimens were collected. Thus, participants contributed 2 diary periods per year and up to 5 diary periods during the 27-month follow-up period.

Diaries and self-obtained specimens were collected on a weekly basis by study personnel, usually at the participants' homes. Diaries assessed whether sexual intercourse occurred on a given day and, if so, whether a condom was used. Participants received $2 for each completed diary and $5 for each vaginal specimen. During a given diary period, vaginal specimens were frozen at –20°C until the final week of diary collection. Specimens were then tested for STI as described later. All infections were treated at quarterly interviews unless the participant sought out treatment owing to concerns or symptoms.

TYPE-SPECIFIC HPV ASSAY

All cervical and vaginal specimens were tested for HPV using a polymerase chain reaction (PCR)/reverse blot strip assay (Roche Diagnostics, Indianapolis, Ind).[21,22] This assay uses nondegenerate primer pairs to amplify 19 oncogenic HPV types (types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 55, 56, 58, 59, 68, 73, 82, 83, and 84) and 8 nononcogenic HPV types (types 6, 11, 40, 42, 53, 54, 57, and 66).[23] To determine specimen adequacy, the GH20/PC04 human β-globin target is coamplified with HPV sequences. Reactions were amplified in a PerkinElmer TC9600 Thermal Cycler (PerkinElmer, Foster City, Calif) as previously described.[23] DNA-positive and -negative specimens were included in each assay as controls.

Reverse blot strip assays used a reference ink line and probe lines for 27 individual HPV genotypes and 2 concentrations of the β-globin control probe.[21] Bovine serum albumin–conjugated probes for each HPV type are deposited in a single line for each of the HPV types. Hybridization and visual detection of PCR products bound to immobilized probes was performed as described earlier.[4,23]

DETECTION OF OTHER STI

Cervical and vaginal swab specimens were also evaluated for the presence of *C trachomatis*, *Neisseria gonorrhoeae,* and *Trichomonas vaginalis*. *C trachomatis* and *N gonorrhoeae* infections were identified using the Amplicor (Roche Diagnostics) *C trachomatis/N gonorrhoeae* PCR assay. Detection of *T vaginalis* DNA was performed using the Amplicor *C trachomatis/N gonorrhoeae* PCR assay with the following modifications. Samples were processed for amplification according to the manufacturer's instructions using microwell plates coated with a *T vaginalis*–specific probe.[24]

Because of the high specificity of nucleic acid amplification tests, any specimen testing positive for *C trachomatis* or *T vaginalis* was considered to represent an infection. However, a lower specificity for *N gonorrhoeae* infections is now well documented.[25,26] For this reason, all specimens positive (all women who tested positive were treated) for *N gonorrhoeae* by the Amplicor *C trachomatis/N gonorrhoeae* PCR assay were initially confirmed by 1 or more of the following tests: culture, BDProbe Tec (Becton, Dickinson, and Company, Franklin Lakes, NJ), *opa*- or *ccB*-based PCR,[27] or GENPROBE Aptima (GENPROBE, Inc, San Diego, Calif). Specimens were characterized as *N gonorrhoeae* infection only when confirmatory test results were also positive.

The STI measures assessed both prevalent (any time during the study) and concurrent infections (during an HPV infection). Prevalent measures assessed any occurrence of *C trachomatis*, *N gonorrhoeae*, or *T vaginalis* during the study period. Concurrent infections were defined as those occurring within the same period as a specific HPV infection.

SEXUAL AND CONTRACEPTIVE BEHAVIORS

Relevant demographic, behavioral, and clinical information were obtained from interviews and diaries, including enrollment age, race (self-designated), sexual behaviors, and contraceptive and condom use behaviors.

Sexual behaviors included age at first sexual intercourse, number of sex partners, coital frequency, and condom use. The exact numbers for coital frequency and condom use were calculated from self-reports about coitus and condom use over the last

3 months using both the diaries and/or quarterly interviews depending on the time and duration of the infection. Sexual partners were the exact number of partners reported during a specific HPV infection. Initial analyses showed that number of partners was highly skewed. Therefore, number of partners was dichotomized at the sample median (as ≤1 vs ≥2 partners). Coital frequency was a continuous variable based on the number of coital events recorded during a specific HPV infection.

Condom use was defined as the proportion of condom-protected coital events during the duration of a specific HPV infection. If no coitus occurred during a specific HPV period, protection was defined as 100%. Dropping out periods of no coital activity would potentially hamper the ability to look at noncoital influences on HPV persistence. Since condom use behavior was contingent on the occurrence of coitus, assuming 100% protection for an infection period without coitus may confound the effect of condom use with that of no coitus. To ensure the validity of the analysis, we assessed the effect of condom use in both the full sample and the subsample containing only the infection periods where coitus had been reported. Because the percentage of condom-protected events had a bimodal distribution with large clusters near 0% and 100% use, condom use was dichotomized based on the sample median to "less condom use" (ie, <60% of coital events) vs "more condom use" (ie, condom use >60%). Measures of contraceptive use included self-reported use of oral contraceptive pills or depot medroxyprogesterone acetate. Participants' medical records were reviewed to verify prescription of oral contraceptive pills and injection of depot medroxyprogesterone during the period in which an HPV infection occurred.

STATISTICAL ANALYSIS

The primary outcome variable was duration (in days) of infection by a specific HPV type. For a given infection, duration was calculated as the time between the initial onset and last detection of a specific HPV type. Prevalent infections at enrollment and incident infections were used for the analysis. Human papillomavirus infection was defined as 2 or more positive specimens for a specific HPV type. An infection with a type-specific HPV was considered to have cleared when the last positive specimen was followed by at least 2 negative specimens before the end of follow-up. When a positive specimen was obtained within 2 weeks of the end of observation, the duration of that specific infection was censored at the end of the data collection period. In other words, infection was assumed to persist at least as long as the end of the observational period if the specific HPV type was detected within 2 weeks of the end of the observation period. A single subject would contribute more than 1 infection to the analysis if she was coinfected and/or subsequently infected with a different HPV type during the observation period.

Cox regression was used to model the length of a type-specific HPV infection as a function of various sexual behaviors, hormonal contraceptive use, and infection with other STI. Since the critical event for the survival analysis is the end of a type-specific HPV infection, a hazard ratio significantly less than 1.0 implies a reduced likelihood of HPV clearance (ie, virus becomes undetectable) or longer duration of HPV infection. A hazard ratio significantly greater than 1.0, on the other hand, implies increased likelihood of HPV clearance, or shorter duration of HPV infection. Unadjusted Kaplan-Meier estimates were reported to highlight the difference in survival curves under different values of independent variables.

The analysis was performed on type-specific infections. Participants with multiple types of HPV infections, either sequentially or concurrently, would contribute multiple observations. In this research, we modeled multiple infections within the subject as unordered events. To accommodate the within-subject correlation associated with these infections, a random-subject effect with a gamma distribution was introduced into the Cox regression model (gamma frailty model).[28] For model selection, we followed a forward selection procedure with an entry criterion of $P<.05$. Data analyses were conducted using SAS version 8.2 (SAS Institute Inc, Cary, NC) and S-Plus 6.1 (Insightful Corp, Seattle, Wash).

Table. Estimated Hazard Ratios of Viral Clearance Based on 241 Human Papillomavirus (HPV) Infections From a Cohort of 49 Adolescent Women

Variable	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Age at enrollment, y	1.12 (0.87-1.45)	. . .
Race (African American vs others)	1.19 (0.81-1.75)	. . .
Age at first intercourse, y	1.26 (1.11-1.43)	. . .
≤1 Partner during an HPV infection (vs ≥2 partners)	5.45 (3.48-8.54)	5.52 (3.28-9.30)
No. of coital events during an HPV infection	0.98 (0.97-0.99)	0.98 (0.98-0.99)
<60% of coital events protected by condoms during an HPV infection (vs >60% condom use)*	0.43 (0.29-0.65)	0.53 (0.33-0.84)
Oral contraceptive pill use during an HPV infection	1.14 (0.75-1.71)	. . .
DMPA use during an HPV infection	0.82 (0.53-1.25)	. . .
Oncogenic HPV type	0.68 (0.48-0.97)	0.58 (0.39-0.84)
Chlamydia trachomatis during the study†	1.14 (0.65-2.01)	. . .
Neisseria gonorrhoeae during the study†	1.06 (0.63-1.69)	. . .
Trichomonas vaginalis during the study†	1.23 (0.75-2.01)	. . .
C trachomatis coinfection‡	0.30 (0.93-0.46)	0.58 (0.31-0.89)
N gonorrhoeae coinfection‡	0.51 (0.31-0.84)	. . .
T vaginalis coinfection‡	0.27 (0.13-0.43)	0.32 (0.16-0.64)

Abbreviations: CI, confidence interval; DMPA, depot medroxyprogesterone acetate.
*Condom use was dichotomized based on sample median.
†Sexually transmitted infection was detected during study period.
‡Sexually transmitted infection was detected during the HPV infection.

RESULTS

Participants' mean age at enrollment was 15.3 years, and 85% reported race as African American. Most participants (57 of 60) reported prior sexual experience at enrollment. Mean (SD) age at first coitus among the sexually experienced was 13.2 (1.7) years.

The mean duration of follow-up was 2.2 years (range, 2.0-2.4 years). Of the 2458 cervical or vaginal specimens collected, 353 were clinician-obtained cervical swabs (collected every 3 months at the quarterly visit) and 2105 were participants' self-obtained vaginal swabs (col-

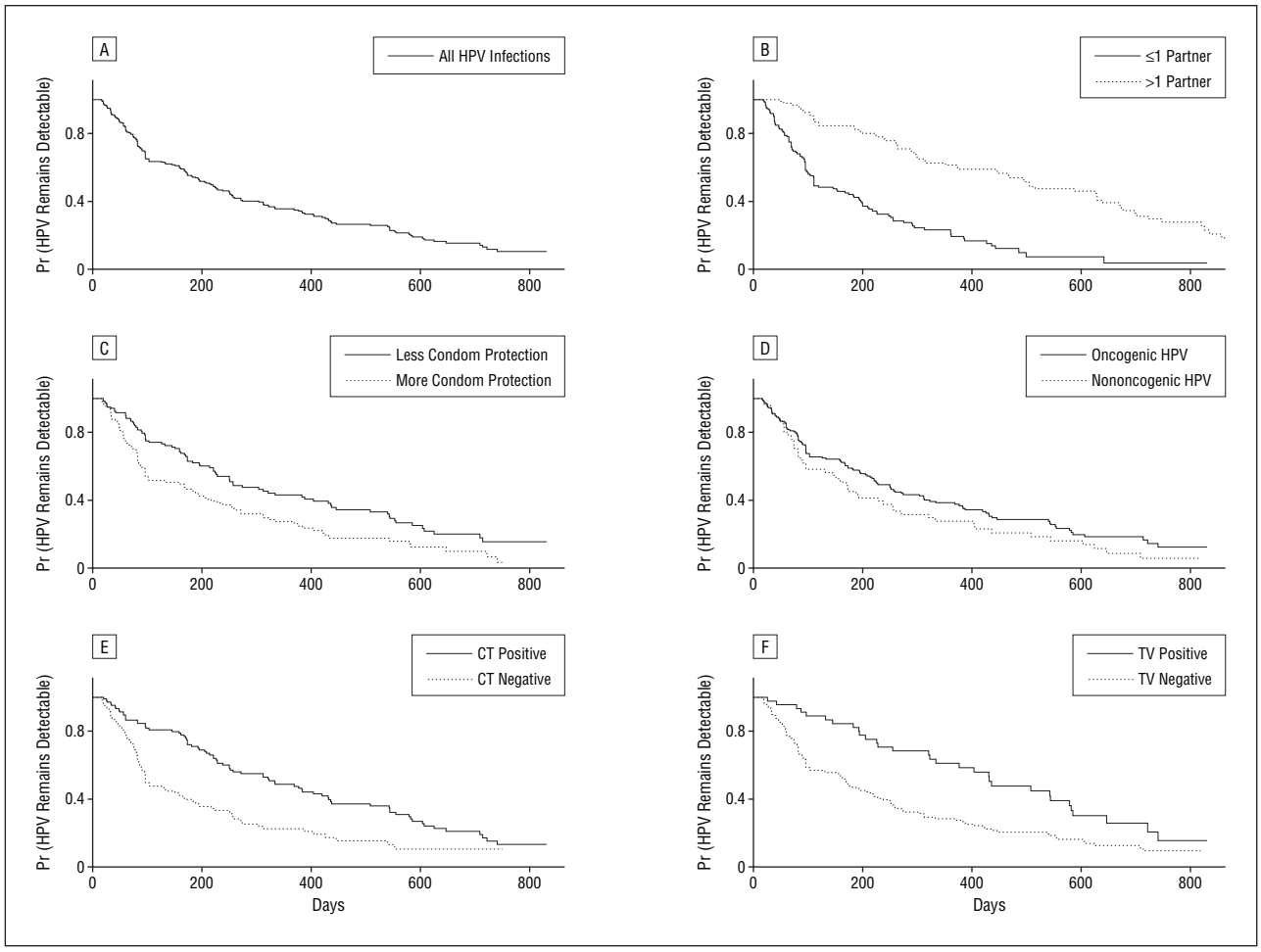

Figure. Kaplan-Meier estimates of the survival of human papillomavirus (HPV) infection (A-F). CT indicates *Chlamydia trachomatis*; TV, *Trichomonas vaginalis;* and Pr, probability.

lected weekly during diary collections). Overall, 2107 (85.7%) of 2458 specimens were positive for β-globin (both the low- and high-abundance bands) and were included in subsequent analyses. As previously reported, the cumulative prevalence of HPV infection was 81.7% (49/60), and those HPV-infected women were used for the survival analyses.[4]

For the 49 women who were HPV positive, the mean number of partners reported during a period associated with HPV infection was 1.7 (median, 1; range, 0-10). The mean number of coital events was 25.8. The median level of condom use was 60.4% during an HPV infection period. The STI coinfection rates during an HPV infection were as follows: 45.4% for *C trachomatis*, 25.4% for *N gonorrhoeae*, and 19.2% for *T vaginalis*. About one third of the participants reported use of oral contraceptive pills or depot medroxyprogesterone injection during the time of an HPV infection.

There were a total of 241 HPV infections with a mean duration of 232.1 days. Of these 241 infections, only 14 were prevalent at the time of enrollment. A total of 168 (70%) of 241 HPV infections were with oncogenic types. Mean duration was 251 days and 189 days for oncogenic and nononcogenic viral types, respectively. Univariate and multivariate risk ratios and 95% confidence intervals are reported in the **Table**.

Kaplan-Meier survival curves for all HPV infections are depicted in **Figure** A. Half of all infections were no longer detected by 210 days after initial detection. Depictions of the association of number of partners, condom use, HPV type, concurrent *C trachomatis* infection, and concurrent *T vaginalis* infection are seen in Figure B-F. Figure B demonstrates HPV infections associated with 1 or no partners (median infection duration, 96 days) ending earlier as compared with infections associated with multiple partners (median infection duration, 437 days). Clearance of HPV was significantly faster during infection periods associated with more frequent condom use (median duration, 58 days) compared with infections associated with less frequent condom use (median duration, 257 days) (Figure C). High-risk HPV infections were slower to clear (median duration, 228 days) than low-risk infections (median, 170 days) (Figure D). The HPV infections associated with concurrent *C trachomatis* infection cleared slower (median duration, 333 days) than those not associated with concurrent *C trachomatis* (median, 96 days) (Figure E). Finally, HPV infections associated with concurrent *T vaginalis* were slower to clear than those not associated with the infection (median time to disappearance was 436 days and 172 days, respectively) (Figure F).

In the multivariable survival analysis, women having only 1 or no sexual partners during an HPV infection were more likely to have shorter periods of HPV detection. Specifically, we estimated that the instantaneous hazard of viral clearance for women with 1 or no sexual partners during HPV infection was 5.52 times that of women with multiple partners, after controlling for the effects of other covariates (adjusted hazard ratio [AHR], 5.52 [95% confidence interval (CI), 3.28-9.30]). Clearance of HPV was less likely in women who had coitus at a higher frequency than the sample median level while infected (AHR, 0.98 [95% CI, 0.98-0.99]); women who used condoms for less than 60% of coital events while infected were less likely to have early clearance compared with women who used condoms more often (AHR, 0.53 [95% CI, 0.33-0.84]); and HPV clearance was also less likely in those women infected by an oncogenic HPV type (AHR, 0.58 [95% CI, 0.39-0.84]) and those concurrently infected with *C trachomatis* (AHR, 0.58 [95% CI, 0.31-0.89]) or *T vaginalis* (AHR, 0.32 [95% CI, 0.16-0.64]). Age at first sex and concurrent *N gonorrhoeae* infection were associated with longer periods of HPV infection in univariate but not multivariable models. Prevalent STI, concurrent oral contraceptive pill use, or concurrent depot medroxyprogesterone use were not associated with duration of the infection. When alternative analyses were performed limited to periods when sex occurred during an HPV infection (this resulted in 40 fewer infection periods), the effect of condom use remained significant in the subsample (risk ratio, 0.58 [95% CI, 0.35-0.97]).

COMMENT

Potentially modifiable factors—sexual behaviors, less frequent condom use, and concurrent sexually transmitted infections—were associated with longer periods of detectable genital HPV infection among adolescent women. Given the importance of viral persistence in the pathogenesis of HPV-associated neoplasia, these findings may have substantial clinical and public health implications. Although persistence of HPV was not assessed directly, potential factors that influence clearance (ie, longer or shorter periods of detection) may likely also be associated with persistence. Interventions designed to influence HPV clearance—for example, to reduce number of sexual partners, increase condom use, and improve STI screening and treatment—might be similar to those already shown to be effective for reducing rates of incident STI.[29] Even with the eventual development of an HPV vaccine that protects against multiple high-risk HPV types, interventions to increase the clearance of HPV infection could influence care of women who are not immunized because of lack of vaccine access or vaccine failure or those who already had been infected with HPV.

Although mechanisms by which sexual behaviors and concurrent STI influence the clearance of HPV infection are not yet well understood, roles for local immune changes and for cervical inflammation are likely.[30] Semen in the female genital tract is associated with a marked postcoital inflammatory response in which transforming growth factor β appears to play an important role in inducing local immune hyporesponsiveness.[31] Our data linking increased levels of condom use with increased clearance of HPV infection are also consistent with observations that condom use is associated with faster regression of cervical intraepithelial neoplasia.[32]

Both *T vaginalis*[33] and *C trachomatis*[17,34] are associated with cervical cancer and its precursor, cervical dysplasia. Cervical inflammation could explain the association of concurrent *C trachomatis* or *T vaginalis* infection with duration of HPV infection.[30] Inflammation associated with these coinfections may favor a cytokine milieu compatible with prolonged HPV infection.[35]

Several limitations should be noted in considering these data. First, the sample represents a relatively small cohort of intensely studied young women. However, the sample itself was not selected on the basis of sexual activity, STI risk behaviors, contraceptive use, or HPV infection status. Thus, our results are not likely attributable to selection for specific factors that might be relevant in other populations. Second, we did not measure cigarette use, which has been linked to HPV persistence and cervical neoplasia in other studies.[12,36] Cigarette smoking is almost certainly an important risk factor for HPV persistence but it is unlikely that the range of factors identified in this study are simply surrogates for the unmeasured effect of smoking. A final limitation is the use of clearance of HPV infection as an outcome rather than a more definitive clinical outcome, such as cervical dysplasia. The incidence of higher-grade cervical dysplastic lesions is relatively low, ultimately requiring a much larger cohort to produce statistically stable estimates.[4] This does not negate the findings and impact that they could have on reducing viral infections and the potential for understanding viral persistence.

Viral clearance of HPV, and potentially persistence, appears to be a complex interaction of sexual behaviors, coexisting genital infections, and viral characteristics. This means that not only is HPV infection persistence a potentially preventable condition but HPV-related cancers may be preventable as well. Effectiveness of condoms has been questioned for some STIs, especially for HPV. The data presented suggest a strong role for condom use and strengthen the need for traditional public health approaches to reduce sexual risk behaviors and increase STI screening (and treatment) as advocated by others.[37,38]

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Correspondence: Darron R. Brown, MD, Emerson Hall, Room 435, 545 Barnhill Dr, Indiana University School of Medicine, Indianapolis, IN 46202 (darbrow@iupui.edu)
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Correction

Error in E-mail Address. In the article "Hearing Screening at Well-Child Visits" by Halloran et al published in the October issue of the ARCHIVES (2005;159:949-955), an incorrect e-mail address was given. On page 955 in the correspondence address, the correct e-mail address for Dr Halloran is dhallor2@slu.edu.