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Risk Factors for Human Papillomavirus Infection and Abnormal Cervical Cytology Among Perinatally Human Immunodeficiency Virus-Infected and Uninfected Asian Youth

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Background. Infection with high-risk human papillomavirus (HR-HPV) may be higher in perinatally human immunodeficiency virus (HIV)–infected (PHIV) than HIV-uninfected (HU) adolescents because of long-standing immune deficiency.

Methods. PHIV and HU females aged 12–24 years in Thailand and Vietnam were matched by age group and lifetime sexual partners. At enrollment, blood, cervical, vaginal, anal, and oral samples were obtained for HPV-related testing. The Wilcoxon and Fisher exact tests were used for univariate and logistic regression for multivariate analyses.

Results. Ninety-three PHIV and 99 HU adolescents (median age 19 [18–20] years) were enrolled (June 2013–July 2015). Among PHIV, 94% were currently receiving antiretroviral therapy, median CD4 count was 593 (392–808) cells/mm^3, and 62% had a viral load <40 copies/mL. Across anogenital compartments, PHIV had higher rates of any HPV detected (80% vs 60%; $P = .003$) and any HR-HPV (60% vs 43%, $P = .02$). Higher proportions of PHIV had abnormal Pap smears (eg, atypical squamous cells of unknown significance [ASC-US], 12% vs 14%; low-grade squamous intraepithelial neoplastic lesions, 19% vs 1%). After adjusting for ever being pregnant and asymptomatic sexually transmitted infections (STI) at enrollment, PHIV were more likely to have HR-HPV than HU (odds ratio, 2.02; 95% confidence interval, 1.09–3.77; $P = .03$).

Conclusions. Perinatal HIV infection was associated with a higher risk of HR-HPV and abnormal cervical cytology. Our results underscore the need for HPV vaccination for PHIV adolescents and for prevention and screening programs for HPV and other STIs.

Keywords. HIV; human papillomavirus; adolescent; perinatal; sexually transmitted infections.

Human immunodeficiency virus (HIV) treatment coverage of the estimated 190 000 adolescents aged 10–19 years living with HIV in the Asia-Pacific has been low, with less than one-third accessing appropriate antiretroviral therapy (ART) [1]. There is a growing generation of perinatally infected adolescents transitioning into adult life and at risk for other sexually transmitted infections (STIs) [2, 3]. One of the world's most commonly acquired STIs is human papillomavirus (HPV), the primary cause of cervical and anal cancers, which has been shown to be more persistent and pathogenic in HIV-infected younger and older women [4–6].

Younger women may be more vulnerable to HPV due, in part, to immaturity of the cervical tissue as it transitions from metaplastic to squamous epithelium during that period of life [7]. While HIV-uninfected (HU) adolescents and young women frequently have regression of low-grade squamous intraepithelial neoplastic lesions (LSIL), HIV alters the dynamics of HPV infection, leading to prolonged infection and more frequent precancerous lesions. These risks remain even after immunologic recovery while on ART [8, 9] and may be greater in the current generation of perinatally HIV-infected young women, who were more likely to start ART later in childhood, compromising immune system development [10–12].

However, while vaccination now offers an effective prevention intervention in higher-income settings, most Asian countries lack a national policy to support HPV vaccination [13]. We conducted an observational study to assess the impact of perinatally acquired HIV (PHIV) on HPV coinfection and cervical cytologic and histologic outcomes among young Asian women.

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METHODS

The HPV in Adolescents Study is a longitudinal, observational, cohort study in Thailand and Vietnam to compare patterns of acquisition and clearance of HPV infection among PHIV and HU females and males, and associated cervical cytology and histologic squamous intraepithelial neoplasia in females. The methods for the female component of this study are described below.

Study Participants

PHIV and HU female adolescents and young adults aged 12–24 years with a history of vaginal intercourse were recruited at 5 study sites: Thailand—HIV-NAT-Thai Red Cross AIDS Research Centre, and Siriraj Hospital Mahidol University both in Bangkok, and Chiang Rai Prachanukroh Hospital in Chiang Rai, and Vietnam—Children's Hospital 1 and Hung Vuong Hospital, both in Ho Chi Minh City. All Thai sites and Children's Hospital 1 were providing routine HIV care to the PHIV youth invited to participate in the study. PHIV and HU participants were matched by age group (12–15, 16–18, 19–21, 22–24 years) and number of lifetime partners (≤3 or >3). Participants were excluded if they were pregnant at the screening visit, if they had an untreated symptomatic STI (except genital warts), or had received prior doses of HPV vaccine and if they were unable to independently complete the study's audio computer-assisted self-interview. Individuals were excluded if they were behaviorally HIV infected or if they were HIV uninfected with other chronic diseases or were using medications associated with compromised immune function.

Study Procedures

Potential study participants provided consent and were then screened at the local study sites. Eligible nonpregnant PHIV and HU females proceeded with baseline study visits that included clinical and sexual behavior assessments, blood testing (complete blood count, alanine transaminase, creatinine, fasting lipids, rapid plasma reagin (RPR) or venereal disease research laboratory (VDRL) tests with confirmatory test, CD4 and HIV RNA for PHIV, HIV antibody for HIV uninfected, urine collection (pregnancy), oral rinse, and anogenital evaluation.

Vaginal, cervical, and anal samples were obtained and placed in separate liquid-based cytology (LBC) containers (ThinPrep PAP test, Hologic, Inc., Massachusetts) for processing. Oral wash and cytology fluid were stored at −20°C to −70°C prior to shipment to the study's central laboratory at the Thai Red Cross AIDS Research Centre. Other routine blood, urine pregnancy, and HIV-related testing (antibody, CD4, HIV RNA) were performed at study site laboratories.

HPV and Other STI Testing

Cervical cytology and histology were evaluated at Chulalongkorn University, Bangkok, Thailand. Chlamydia and gonorrhea (Abbott RealTime CT/NG assay, Abbott Molecular Inc., Illinois; Cobas4800 CT/NG test, Roche Molecular Systems, Inc., New Jersey), herpes simplex virus 2 (HSV-2; HSV I & II Typing Real Time PCR kit, Shanghai ZJ Bio-Tech Co. Ltd.), syphilis serology screening (RPR, Becton, Dickinson and Company, Maryland; confirmation testing TP-PA, Fujirebio Inc., Tokyo, Japan), and HPV-related testing were conducted at the central laboratory.

LBC fluid from the 3 anogenital compartments and oral rinses were tested using the LINEAR ARRAY test (LA HPV GT, Roche Molecular Systems, Inc.) to identify 13 high-risk HPV (HR-HPV) DNA genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) and 24 other genotypes (6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 66, 67, 69, 70, 71, 72, 73 [MM9], 81, 82 [MM4], 83 [MM7], 84 [MM8], IS39, CP6108). Cervical LBC fluid samples were used to detect E6 and E7 mRNA by flow cytometric analysis (HPV OncoTect E6, E7 mRNA test, incellDx, CA) for 14 HR-HPV types (16, 18, 31, 33, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73).

Cytology and Histology

Cervical cytology results were classified using the 2001 Bethesda system as normal, atypical squamous cells of unknown significance (ASC-US), atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (ASC-H), LSIL, high-grade squamous intraepithelial lesion (HSIL), or carcinoma [14]. Histology results were categorized as atypia, cervical intraepithelial neoplasia (CIN) 1, CIN 2, CIN 3, carcinoma in situ, and invasive carcinoma.

Participants meeting colposcopy referral criteria were scheduled for additional follow-up. Specifically, this included those with ASC-US and concomitant infection with a HR-HPV type or detection of E6/E7 mRNA, LSIL, ASC-H, HSIL, and atypical glandular cells or carcinoma on cervical cytology. Cervicovaginal abnormalities identified during a colposcopy visit were biopsied for histologic analysis.

Ethics Reviews

The study protocol and informed consent and assent documents were approved by the institutional review boards at the coordinating center (amfAR/TREAT Asia) and at each participating study site. Consent procedures were conducted in the local language (Thai or Vietnamese) by trained study staff. Guardian consent and adolescent assent procedures were followed for participants aged <18 years who could not legally consent for themselves. These participants were formally consented for ongoing study participation after turning 18 or otherwise reaching the age of maturity according to local law.

Statistical Methods

Power calculations were based on the prevalence of vaginal HPV in HIV-positive (73%) and HU (43%) female adolescents in the US REACH (Reaching for Excellence in Adolescent Care and Health) cohort [15]. Assuming a baseline prevalence of 40% in the HU adolescents, with 90 participants in each group we

would have 80% power to detect a 21% difference in prevalence between groups, with 80% power at a 2-sided significance level of 5%. Categorical covariates were compared between study groups using a Wilcoxon test for continuous covariates and Fisher exact test for categorical covariates. Logistic regression was used to assess the association between demographic and behavioral characteristics and the presence of any cervical, vaginal, or anal HR-HPV. Factors with $P < .1$ in univariate models were adjusted for in a multivariate analysis. Statistical analysis was performed with Stata, version 14 (Statacorp LP, College Station, Texas).

RESULTS

Participant Characteristics

Ninety-three PHIV and 99 HU adolescents with a median age of 19 (18–20) years were enrolled between June 2013 and July 2015. PHIV participants were less likely to live with biological parents (26% vs 62%) and more likely to be single or double orphans (81% vs 24%). Approximately equal proportions of both groups were living with a partner or husband (26% vs 19%) and working to support themselves (45% vs 31%). The majority were currently in or had completed secondary school (77% vs 70%). Among PHIV participants, 94% were currently receiving first- or second-line ART, with a median duration from ART start of 4.1 (interquartile range [IQR], 2.5–6.5) years. The median CD4 cell count at enrollment was 593 (392–808) cells/mm^3, and 62% had a viral load <40 copies/mL. One-third (37%) reported some difficulties with adherence, and the median adherence rate in the previous month was 97%.

Sexual Behaviors and Substance Use

In both groups, the median (IQR) number of lifetime partners was 2 (1–3), and partners in the previous 6 months was 1 (1–1); 4% of PHIV and 1% of HU participants reported ever having receptive anal sex, and approximately 22% of both groups reported ever having receptive oral sex (Table 1). More PHIV than HU participants reported consistently using condoms with vaginal sex in the past 6 months (33% vs 11%); the majority in both groups reported sometimes or never (65% vs 85%) using condoms. One-third of PHIV and 44% of HU adolescents reported previous pregnancies.

Fewer PHIV participants had tried alcohol (77% vs 90%), cigarettes (29% vs 44%), or other drugs (8% vs 19%); 1 PHIV participant reported ever having injected drugs (Supplementary Table 1). Similar proportions (17% vs 20%) reported having unsafe sex after using alcohol or other substances.

HPV and Asymptomatic STI at Study Entry

Infection with *Chlamydia trachomatis* was the most common prevalent asymptomatic STI, present in 26% of PHIV and 20% of HU adolescents. A significantly higher proportion of PHIV participants had gonorrhea (5% vs 0%, $P = .03$), 2% of both groups had a reactive VDRL (confirmed by *Treponema pallidum* hemagglutination assay testing), and no PHIV but 3% of HU participants had HSV-2 infection.

Cervical HPV infection of any type was more prevalent in the PHIV group than in the HU group: 62% vs 40% had any HPV detected ($P = .003$), and 43% vs 29% had at least 1 HR-HPV genotype detected ($P = .05$). Similar levels of HR-HPV detection were found in samples collected from the vagina (49% vs 35%), but a significantly higher proportion of PHIV participants had HR-HPV detected in the anus (42% vs 23%, $P = .008$; Table 1). In any anogenital compartment, PHIV participants had significantly higher rates of any HPV detected (80% vs 60%; $P = .003$) and any HR-HPV (60% vs 43%, $P = .02$) than HU participants. HPV infection in the oral cavity was present in 11% of PHIV and 8% of HU adolescents ($P = .64$). The most commonly detected HR-HPV genotypes in the cervix, vagina, and anus included types 16, 18, 52, and 59 (Figure 1).

Cervical Cytology

Normal cervical cytology was present in 67% of PHIV participants and 84% of HU participants (Figure 2). Higher proportions of PHIV participants had abnormal Pap smears compared to HU participants (ASC-US, 12% vs 14%; LSIL, 19% vs 1%; HSIL, 1% vs 1%; ASC-H, 1% vs 0; $P < .001$). Of the 40 (28 PHIV, 12 HU) participants who met criteria for referral, 23 (58%; 19 PHIV, 4 HU) underwent colposcopic examination with or without biopsy within 24 weeks of their baseline cytology visit (Supplementary Table 2). Among those who did not have colposcopies, 9 were PHIV (5 with ASC-US; 1 with ASC-H; 3 with LSIL) and 8 were HU (7 with ASC-US; 1 with HSIL). Reasons for missed colposcopies included delayed referrals (29%) and temporary or permanent loss to follow-up (42%). The colposcopic findings among the PHIV participants included 42% with normal evaluations, 26% with condyloma acuminata, 16% with changes consistent with HPV infection, and 11% with CIN 1. Three (75%) of the 4 HU participants with colposcopies had HPV-related changes. Of the 9 (39%) participants who had biopsies taken, 3 had CIN 1 and 1 had CIN 3; all were PHIV.

Association Between Participant Demographic and Behavioral Characteristics and HR-HPV in Anogenital Compartments

We used logistic regression to assess associations between participant characteristics and behaviors and any detected HR-HPV infection in the cervix, vagina, or anus (Table 2). In a univariate analysis, HIV status, increasing number of lifetime partners, and having an asymptomatic STI diagnosed at enrollment were associated with a significantly higher odds of having HR-HPV, while ever being pregnant was associated with a reduced odds. After adjusting for ever having been pregnant and having an asymptomatic STI at enrollment in a multivariate model, PHIV participants were more likely to have HR-HPV than HU adolescents (odds ratio [OR], 2.02; 95% confidence interval [CI], 1.09–3.77; $P = .03$). Overall,

Table 1. Participant Characteristics at Study Entry (N = 192)

Characteristic	Total (n = 192)	Perinatally HIV Infected (n = 93)	HIV Uninfected (n = 99)	*P* Value
Age, years	19 (18–20)	19 (17–20)	19 (18–20)	.36
Ethnicity				1.0
Thai	177 (92%)	86 (92%)	91 (92%)	…
Vietnamese	15 (8%)	7 (8%)	8 (8%)	…
Living situation				<.001
One or both parents	84 (44%)	24 (26%)	60 (61%)	…
Relatives	44 (23%)	33 (35%)	11 (11%)	…
Partner	43 (22%)	24 (26%)	19 (19%)	…
Alone	15 (8%)	8 (9%)	7 (7%)	…
Other, did not answer	6 (3%)	4 (4%)	2 (2%)	…
Orphan status				<.001
Not an orphan	87 (45%)	13 (14%)	74 (75%)	…
Maternal or paternal orphan	55 (29%)	34 (37%)	21 (21%)	…
Double orphan	44 (23%)	41 (44%)	3 (3%)	…
Unknown	6 (3%)	5 (5%)	1 (1%)	…
Current/highest education				.36
Primary school	20 (10%)	10 (11%)	10 (10%)	…
Secondary school	141 (73%)	72 (77%)	69 (70%)	…
Beyond secondary school	30 (16%)	11 (12%)	19 (19%)	…
Employment/school				.003
Currently working	73 (38%)	42 (45%)	31 (31%)	…
In school	78 (41%)	41 (44%)	37 (37%)	…
Neither	40 (21%)	10 (11%)	30 (30%)	…
Type of sexual relationships				…
Female–Male	184 (99%)	88 (100%)	96 (99%)	1.00
Female–Female	13 (7%)	8 (9%)	5 (5%)	.39
Did not answer	7 (4%)	5 (5%)	2 (2%)	…
Prior sexual activity by route				
Anal receptive	5 (3%)	4 (4%)	1 (1%)	.20
Oral receptive	42 (22%)	19 (21%)	23 (23%)	.73
Lifetime partners	2 (1–3)	2 (1–3)	2 (1–3)	.76
Partners in past 6 months	1 (1–1)	1 (1–1)	1 (1–1)	.74
Monthly frequency of sex in past 3 months				.34
≤5 times	107 (56%)	56 (60%)	51 (52%)	…
6–10 times	32 (17%)	11 (12%)	21 (21%)	…
11–20 times	13 (7%)	5 (5%)	8 (8%)	…
>20 times	21 (11%)	11 (12%)	10 (10%)	…
Did not answer	19 (10%)	10 (11%)	9 (9%)	
Condom use with vaginal sex in past 6 months				<.001
Always	42 (22%)	31 (33%)	11 (11%)	…
Sometimes	93 (48%)	50 (54%)	43 (43%)	…
Never	52 (27%)	10 (11%)	42 (42%)	…
No recent sex	5 (3%)	2 (2%)	3 (3%)	…
Ever been pregnant	75 (39%)	31 (33%)	44 (44%)	.14
Asymptomatic sexually transmitted infections at baseline				
Chlamydia trachomatis	44 (23%)	24 (26%)	20 (20%)	.39
Neisseria gonorrhoea	5 (3%)	5 (5%)	0 (0%)	.03
Syphilis	4/190 (2%)	2/92 (2%)	2/98 (2%)	1.0
Herpes simplex virus 2	3 (2%)	0 (0%)	3 (3%)	.25
Any cervical HPV	98 (51%)	58 (62%)	40 (40%)	.003
Any cervical HR HPV	69 (36%)	40 (43%)	29 (29%)	.05
Any vaginal HPV	110/190 (58%)	62/91 (68%)	48 (48%)	.01
Any vaginal HR HPV	80/190 (42%)	45/91 (49%)	35 (35%)	.06
Any anal HPV	94/191 (49%)	54 (58%)	40/98 (41%)	.02
Any anal HR HPV	62/191 (32%)	39 (42%)	23/98 (23%)	.008
Any anogenital HPV	133 (69%)	74 (80%)	59 (60%)	.003
Any anogenital HR HPV	99 (52%)	56 (60%)	43 (43%)	.02
Any oral HPV	18/190 (9%)	10/91 (11%)	8 (8%)	.62
Any oral HR HPV	9/190 (5%)	5/91 (5%)	4 (4%)	.74

Characteristics are described as median (interquartile range or N [%]). Percentages are rounded and may not total 100%. Where test results were invalid or not performed, the denominator is shown.

Abbreviations: HIV, human immunodeficiency virus; HPV, human papillomavirus; HR, high risk.

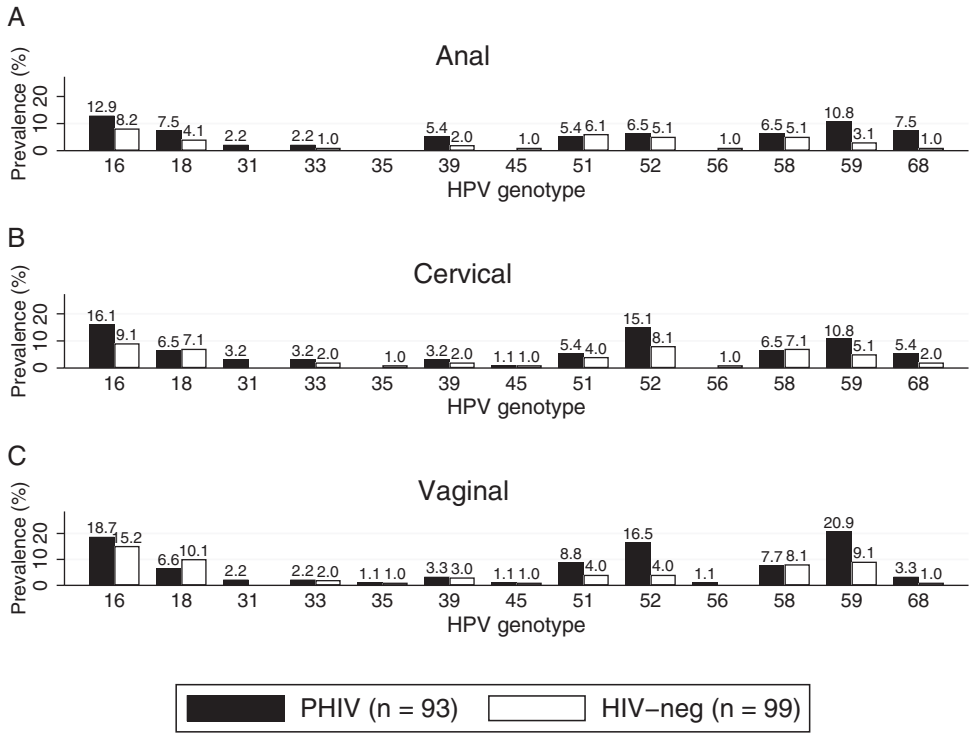

Figure 1. Prevalence of individual high-risk human papillomavirus subtypes by anatomical site. Abbreviations: HIV, human immunodeficiency virus; HIV-neg, HIV uninfected; HPV, human papillomavirus; PHIV, perinatally HIV infected.

compared to those with 1 lifetime partner, those with ≥2 partners had an increased odds of HR-HPV infection (OR, 3.46; 95% CI, 1.78–6.71; $P < .001$). In a subgroup analysis of HIV-specific characteristics in PHIV participants, we found no associations between HR-HPV and current or nadir CD4 count or current viral load.

DISCUSSION

Half of our cohort had prevalent HR-HPV infection, and PHIV adolescent females were more frequently infected with HR-HPV across anogenital compartments and had greater cervical dysplasia on Pap smear than HU adolescents (60% vs 43%). Although our rate of anogenital HR-HPV infection among PHIV participants is similar to those reported among older HIV-infected women and behaviorally HIV-infected youth from other countries [16–19], it is 2–3 times that observed in older HIV-infected Thai women (19%–35% at median ages of 25–40 years) [20–22]. The scale of this difference emphasizes the greater vulnerability of Asian PHIV adolescents to long-term cancer risk. One-third of our adolescents had abnormal cervical cytology, which was consistent with an earlier US PHIV cohort (30%; mean age 19 years) [23] but higher than a parenterally infected Romanian cohort (25%; mean age 23 years) [24]. Furthermore, on colposcopy, condyloma acuminata and CIN 1 and CIN 3 on either visual inspection or biopsy were only detected among PHIV participants (42% vs 0% of those evaluated), raising concerns about the relative severity of disease they experience.

Although recognized as the world's most common STI, the global impact of HPV infection is largely hidden until it causes anogenital and oral cancers decades later. Younger women are more likely to acquire initial and multiple genotype infections due, in part, to cervical ectopy [15, 25]. However, these early infections generally self-resolve, which has led to recommendations to screen them less frequently and to avoid aggressive management for less advanced dysplasia [26]. However, HIV's weakening of cellular immunity is considered a key reason why

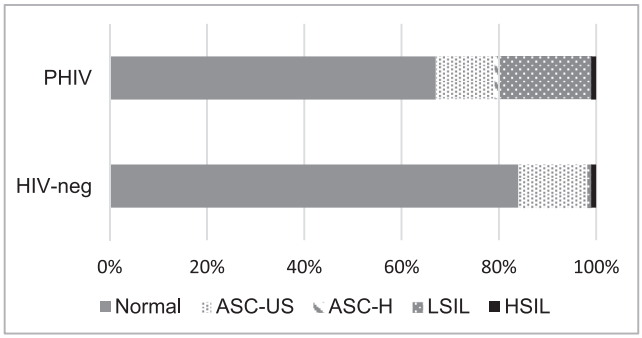

Figure 2. Cervical cytology results. P for difference between groups <0.001. Abbreviations: ASC-H, atypical squamous cells, cannot exclude HSIL; ASC-US, atypical squamous cells of unknown significance; HIV, human immunodeficiency virus; HIV-neg, HIV uninfected; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; PHIV, perinatally HIV infected.

Table 2. Factors Associated With Any High-Risk Human Papillomavirus Genotype at Baseline Study Visit

	Univariate		Multivariate	
Characteristic	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Study group		.02		.03
HIV uninfected	1 (ref)		1 (ref)	
Perinatally HIV infected	1.97 (1.11–3.50)		2.02 (1.09–3.77)	
Age (years)		.83		
13–16	1.34 (0.52–3.43)		…	
17–19	1.12 (0.61–2.05)		…	
20–24	1 (ref)		…	
Orphan status		.57		
Not an orphan	1 (ref)		…	
Maternal orphan	1.79 (0.71–4.51)		…	
Paternal orphan	0.68 (0.29–1.56)		…	
Double orphan	2.07 (0.98–4.39)		…	
Unknown	0.21 (0.02–1.91)		…	
Highest education		.55		
Primary school	1 (ref)		…	
Secondary school	1.28 (0.50–3.27)		…	
Beyond secondary school	1.83 (0.58–5.76)		…	
Condom use with vaginal sex in past 6 months		.45		
Always/no sex in past 6 months	1 (ref)		…	
Sometimes/never	1.29 (0.67–2.49)		…	
Employment/school status		.48		
In school	1 (ref)		…	
Working	1.48 (0.78–2.82)		…	
Neither	1.27 (0.59–2.74)		…	
Used alcohol in past 3 months	1.03 (0.58–1.82)	.92	…	
Smoked in past 3 months	1.02 (0.42–2.43)	.97	…	
Used other drugs in past 3 months	1.91 (0.46–7.89)	.36	…	
Lifetime number of sexual partners		<.001		<.001
1	1 (ref)		1 (ref)	
≥2	3.90 (2.09–7.28)		3.46 (1.78–6.71)	
Sexual partners in past 6 months		.28		
None	1 (ref)		…	
1	0.73 (0.24–2.20)		…	
≥2	1.88 (0.39–9.01)		…	
Ever had unsafe sex after using alcohol or other drugs	1.59 (0.76–3.34)	.21	…	
Ever been pregnant	0.61 (0.34–1.09)	.09	0.61 (0.32–1.15)	.12
Asymptomatic sexually transmitted infection at week 0 visit	2.72 (1.38–5.36)	.003	1.99 (0.96–4.14)	.06
HIV-specific covariates (perinatally HIV infected only)				
HIV-RNA >40 copies/mL	1.77 (0.73–4.28)	.20	…	
Current CD4 count (cells/mm^3)		.31		
≤350	1 (ref)		…	
351–500	0.48 (0.12–1.98)		…	
>500	1.18 (0.40–3.50)		…	
Nadir CD4 count (cells/mm^3)		.25		
<200	1 (ref)		…	
201–500	0.51 (0.17–1.57)		…	
>500	0.41 (0.13–1.22)		…	

Human papillomavirus detected at cervix, vagina, and/or anus.

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

it is associated with more rapid HPV acquisition after new HIV infection and a 2- to 22-fold higher incidence of invasive cervical cancer [27, 28]. Perinatally acquired HIV and its associated life-long impact on the immune system may consequently put infected adolescents and young women at greater risk of HPV-related diseases.

PHIV youth have been reported to have slower pubertal maturity, later sexual debut, and higher condom use than HU youth

[29–31]. This has made comparisons to sexual health outcomes of the uninfected or the behaviorally infected more complicated, and STI frequencies have been reported to be lower among the perinatally infected [32]. However, when matched for behavior, PHIV females in our study had higher baseline HPV and asymptomatic gonorrhea infection than HU females, despite reporting more regular condom use and less frequent substance use.

There are varying data on how ART impacts the natural history of HPV infection in terms of acquisition, persistence, and disease progression. Studies examining associations with any or longer durations of therapy are confounded by adherence patterns, but ART that effectively controls HIV and leads to immune recovery appears to be beneficial [16, 27, 32]. Although we observed no positive or negative association with ART outcomes, almost all of our PHIV participants were on ART and had high levels of immune reconstitution (median CD4, 593 cells/mm^3), although HIV control in terms of viral suppression was moderate (63%). The small numbers of patients with immune deficiency may have prevented us from being able to detect an association.

HPV vaccination using the quadrivalent vaccine has been shown in the IMPAACT P1085 study to be 90%–100% immunogenic in PHIV children and young adolescents aged 7–12 years with CD4 levels above 15%, but other studies have reported that responses may be reduced in the context of unsuppressed HIV [33–35]. Current recommendations of the Advisory Committee on Immunization Practices are to use a 3-dose series in those with HIV [36]. Unfortunately, the vaccines that can prevent the consequences of HPV are less accessible in the regions where most PHIV youth reside and often do not include catch-up vaccine programs for older adolescents [37]. Thailand started a national HPV vaccination program in August 2017 that provides access to females aged 10–12 years and enrolled in primary school (grade 5) [38, 39]. While an important step forward, this misses the vast majority of PHIV adolescents who have already aged out of this group, such as in our cohort where the majority had evidence of current HR-HPV infection. In addition to implementation of early vaccination programs, supplemental approaches to offer catch-up vaccine to older adolescents, such as Malaysia's program that includes 18-year-olds, are essential if those at greater risk for HPV-related cancers are to be protected [13].

There were limitations in both the conduct of the study and the interpretation of our results. We were unable to enroll younger adolescents, which restricts the generalizability of our findings. Since consent for legal minors aged <18 years required admission of sexual activity, the social and cultural stigma against premarital sexual debut was viewed by site investigators as a deterrent. Social desirability bias could have impacted the reliability of our self-reported sexual behavior risks. We did not evaluate 42% of those meeting colposcopy referral criteria within 24 weeks of their cytology visit. In our routine clinical care settings, colposcopy referrals are even less consistently completed, further emphasizing the importance of preventive vaccination. Importantly, cross-sectional studies of HPV infection do not indicate the duration of infection, which plays a key role in the development of dysplasia. While we attempted to capture risk factors known to be related to both infections in sufficient detail, and our regression analysis adjusted for potential confounders derived from a careful review of the HPV and HIV literature, there remains a risk of unmeasured confounding. Given our pilot data and previous studies demonstrating associations in adults, we believe there is sufficient rationale for the associations we have observed, but additional follow-up to monitor for persistence vs clearance will facilitate further interpretation of the natural history of HPV in this cohort.

Our study showed that PHIV participants in Thailand and Vietnam had higher rates of HR-HPV infection and cervical dysplasia than HU adolescents and young women after matching for age and sexual behavior. While HPV vaccination is the optimal solution to prevent anogenital cancers, the lack of access to HPV vaccines in low- and middle-income countries makes screening to identify those in need of intervention an essential component of comprehensive HIV care for young women. Our results underscore the need for prevention and screening for HPV and other STIs in Asian PHIV adolescents.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. UNICEF. Adolescents under the radar in the Asia-Pacific AIDS response. Bangkok: UNICEF East Asia and Pacific Regional Office, **2015**.
2. Lolekha R, Boon-Yasidhi V, Leowsrisook P, et al. Knowledge, attitudes, and practices regarding antiretroviral management, reproductive health, sexually transmitted infections, and sexual risk behavior among perinatally HIV-infected youth in Thailand. AIDS Care **2015**; 27:618–28.
3. Sohn AH, Hazra R. Old problems for new providers: managing the postpediatric HIV generation. Clin Infect Dis **2017**; 64:1113–4.
4. Adler DH, Wallace M, Bennie T, et al. Cumulative impact of HIV and multiple concurrent human papillomavirus infections on the risk of cervical dysplasia. Adv Virol **2016**; 2016:7310894.

5. Adler DH, Wallace M, Bennie T, et al. Cervical dysplasia and high-risk human papillomavirus infections among HIV-infected and HU adolescent females in South Africa. Infect Dis Obstet Gynecol **2014**; 2014:498048.
6. Clifford GM, de Vuyst H, Tenet V, Plummer M, Tully S, Franceschi S. effect of HIV infection on human papillomavirus types causing invasive cervical cancer in Africa. J Acquir Immune Defic Syndr (1999) **2016**; 73:332–9.
7. Moscicki AB, Ma Y, Jonte J, et al. The role of sexual behavior and human papillomavirus persistence in predicting repeated infections with new human papillomavirus types. Cancer Epidemiol Biomarkers Prev **2010**; 19:2055–65.
8. Mangclaviraj S, Kerr SJ, Chaithongwongwatthana S, et al. Nadir CD4 count and monthly income predict cervical squamous cell abnormalities in HIV-positive women in a resource-limited setting. Int J STD AIDS **2008**; 19:529–32.
9. Carlander C, Wagner P, Svedhem V, et al. Impact of immunosuppression and region of birth on risk of cervical intraepithelial neoplasia among migrants living with HIV in Sweden. Int J Cancer **2016**; 139:1471–9.
10. Chokephaibulkit K, Kariminia A, Oberdorfer P, et al; TREAT Asia Pediatric HIV Observational Database. Characterizing HIV manifestations and treatment outcomes of perinatally infected adolescents in Asia. Pediatr Infect Dis J **2014**; 33:291–4.
11. Lewis J, Payne H, Walker AS, et al. Thymic output and CD4 T-cell reconstitution in HIV-infected children on early and interrupted antiretroviral treatment: evidence from the Children With HIV Early Antiretroviral Therapy trial. Front Immunol **2017**; 8:1162.
12. Picat MQ, Lewis J, Musiime V, et al; ARROW Trial Team. Predicting patterns of long-term CD4 reconstitution in HIV-infected children starting antiretroviral therapy in sub-Saharan Africa: a cohort-based modelling study. PLoS Med **2013**; 10:e1001542.
13. amfAR. Cervical Cancer, Human Papillomavirus (HPV), and HPV Vaccines in Southeast Asia. New York: The Foundation for AIDS Research, **2016**.
14. Kurman R, Solomon DT. The Bethesda system for reporting cervical/vaginal cytologic diagnoses. New York: Springer-Verlag, **1994**.
15. Moscicki AB, Ellenberg JH, Farhat S, Xu J. Persistence of human papillomavirus infection in HIV-infected and -uninfected adolescent girls: risk factors and differences, by phylogenetic type. J Infect Dis **2004**; 190:37–45.
16. Kelly HA, Sawadogo B, Chikandiwa A, et al; HARP Study Group. Epidemiology of high-risk human papillomavirus and cervical lesions in African women living with HIV/AIDS: effect of anti-retroviral therapy. AIDS **2017**; 31:273–85.
17. Thunga S, Andrews A, Ramapuram J, et al. Cervical cytological abnormalities and human papilloma virus infection in women infected with HIV in Southern India. J Obstet Gynaecol Res **2016**; 42:1822–8.
18. Moscicki AB, Ellenberg JH, Vermund SH, et al. Prevalence of and risks for cervical human papillomavirus infection and squamous intraepithelial lesions in adolescent girls: impact of infection with human immunodeficiency virus. Arch Pediatr Adolesc Med **2000**; 154:127–34.
19. Joint United Nations Programme on HIV/AIDS (UNAIDS). Ending AIDS: Progress towards the 90-90-90 targets. Geneva: UNAIDS, **2017**.
20. Bollen LJ, Chuachoowong R, Kilmarx PH, et al. Human papillomavirus (HPV) detection among human immunodeficiency virus-infected pregnant Thai women: implications for future HPV immunization. Sex Transm Dis **2006**; 33:259–64.
21. Delory T, Ngo-Giang-Huong N, Rangdaeng S, et al; PapilloV Study Group. Human papillomavirus infection and cervical lesions in HIV infected women on antiretroviral treatment in Thailand. J Infect **2017**; 74:501–11.
22. Ramautarsing RA, Phanuphak N, Chaithongwongwatthana S, et al. Cervical and anal HPV infection: cytological and histological abnormalities in HIV-infected women in Thailand. J Virus Erad **2015**; 1:96–102.
23. Brogly SB, Watts DH, Ylitalo N, et al. Reproductive health of adolescent girls perinatally infected with HIV. Am J Public Health **2007**; 97:1047–52.
24. Ene L, Voinea C, Stefanescu C, Sima D, Duiculescu D, Mehta SR. Cervical HPV infection in Romanian women infected with HIV during early childhood. Int J STD AIDS **2016**; 27:1079–85.
25. Houlihan CF, Baisley K, Bravo IG, et al. Rapid acquisition of HPV around the time of sexual debut in adolescent girls in Tanzania. Int J Epidemiol **2016**; 45:762–73.
26. Practice Bulletin No. 157: cervical cancer screening and prevention. Obstet Gynecol **2016**; 127:e1–20.
27. Denny LA, Franceschi S, de Sanjosé S, Heard I, Moscicki AB, Palefsky J. Human papillomavirus, human immunodeficiency virus and immunosuppression. Vaccine **2012**; 30(Suppl 5):F168–74.
28. Nowak RG, Gravitt PE, Morrison CS, et al. Increases in human papillomavirus detection during early HIV infection among women in Zimbabwe. J Infect Dis **2011**; 203:1182–91.
29. Ananworanich J, Prasitsuebsai W, Kerr SJ, et al. Cervical cytological abnormalities and HPV infection in perinatally HIV-infected adolescents. J Virus Erad **2015**; 1:30–7.
30. Bellavia A, Williams PL, DiMeglio LA, et al; International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P219/219C Study, and the Pediatric HIV/AIDS Cohort Study (PHACS). Delay in sexual maturation in perinatally HIV-infected youths is mediated by poor growth. AIDS **2017**; 31:1333–41.
31. Williams PL, Abzug MJ, Jacobson DL, et al; International Maternal Pediatric and Adolescent AIDS Clinical Trials P219219C Study and the Pediatric HIVAIDS Cohort Study. Pubertal onset in children with perinatal HIV infection in the era of combination antiretroviral treatment. AIDS **2013**; 27:1959–70.
32. Camacho-Gonzalez AF, Chernoff MC, Williams PL, et al. Sexually transmitted infections in youth with controlled and uncontrolled human immunodeficiency virus infection. J Pediatric Infect Dis Soc **2017**; 6:e22–9.
33. Brophy J, Bitnun A, Alimenti A, et al. Immunogenicity and safety of the quadrivalent human papillomavirus vaccine in girls living with HIV. Pediatr Infect Dis J **2017**. doi: 10.1097/INF.0000000000001874.
34. Kojic EM, Rana AI, Cu-Uvin S. Human papillomavirus vaccination in HIV-infected women: need for increased coverage. Expert Rev Vaccines **2016**; 15:105–17.
35. Levin MJ, Moscicki AB, Song LY, et al. Safety and immunogenicity of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine in HIV-infected children 7 to 12 years old. J Acquir Immune Defic Syndr **2010**; 55:197–204.
36. Meites E, Kempe A, Markowitz LE. Use of a 2-dose schedule for human papillomavirus vaccination—updated recommendations of the advisory committee on immunization practices. Morb Mortal Wkly Rep **2016**; 65:1405–8.
37. Mbulawa ZZA, van Schalkwyk C, Hu NC, et al. High human papillomavirus (HPV) prevalence in South African adolescents and young women encourages expanded HPV vaccination campaigns. PLoS One **2018**; 13:e0190166.
38. Guidelines for the HPV vaccination among grade 5 female students in the Expanded Programme of Immunization. Thailand: Ministry of Public Health, **2016**.
39. Pisuthipan A. To be or not to be vaccinated. Bangkok Post. **2017**.

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