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The role of Chlamydia trachomatis in high-risk human papillomavirus persistence among female sex workers in Nairobi, Kenya

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Abstract

Background—Little is known about risk factors for persistent high-risk HPV (hrHPV) infection in low-income settings, and prior research has not quantified the relative duration of hrHPV infections stratified by risk factors. We compared the duration of hrHPV infection among female sex workers (FSW) by exposure to sexually transmitted infections (STIs), using a highly-sensitive biomarker assay.

Methods—From 2009–2011, 350 FSW enrolled in this longitudinal study. Every three months, sociodemographic and sexual behavior data were collected via questionnaire, and APTIMA assays were used to detect the rRNA of *Chlamydia trachomatis* (CT), *Neisseria gonorrhea* (GC), *Trichomonas vaginalis* (TV), *Mycoplasma genitalium* (MG), and mRNA of the E6/E7 oncoproteins expressed by hrHPV. Among 173 FSW who were infected with hrHPV during the observation period, accelerated failure time models estimated time ratios (TR) for duration of hrHPV infection, comparing FSW infected with STIs at baseline to STI-uninfected FSW.

Results—Median follow-up time was 26.2 months (IQR: 18.8 – 27.5). The median duration of hrHPV infection among all FSW was 9.3 months (95% CI: 9.3, 11.5). The duration of hrHPV infection among FSW infected with CT at baseline was greater than that among FSW who were uninfected (adjusted TR: 1.7, 95% CI: 1.2, 2.6). Among FSW who were co-infected with hrHPV and CT at baseline, the adjusted TR was 3.4 (95% CI: 2.5, 5.4) compared to FSW infected with hrHPV only. No other STI was associated with hrHPV duration.

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Conclusion—Recent or concurrent CT infection was associated with prolonged hrHPV infection among a cohort of Nairobi FSW. Management of CT could reduce risk for hrHPV persistence.

Keywords

hrHPV persistence; female sex workers; sexually transmitted infections; HPV mRNA testing; Chlamydia trachomatis; human papillomavirus; persistence

INTRODUCTION

Over 100 types of human papillomavirus (HPV) have been identified, at least 13 of which are high-risk types that cause high-grade pre-cancerous squamous intraepithelial lesions (HSIL) and subsequent invasive cervical cancer (ICC).[1] While most HPV infections resolve on their own within one year, certain high-risk HPV (hrHPV) types are more likely to persist for longer, such as types 16, 33, and 31.[2] Thus, persistent hrHPV infection is the most important risk factor for the development of ICC.[3] There is currently no standard treatment for hrHPV viral infections, and resource-limited settings often lack the health infrastructure to adequately screen for and treat HSIL and ICC. In Kenya, the Pap test is the primary form of cervical cancer screening, but is generally only available in urban areas and is subject to long delays between screening and obtaining results. Visual inspection with acetic acid is available in resource-limited settings, but outpatient treatment services (e.g. cryotherapy and loop electrosurgical excision procedure) are largely unavailable throughout the country.[4] In the absence of a national HPV vaccination strategy, identifying risk factors for persistent hrHPV can improve resource-efficient cervical cancer prevention.

Sexually transmitted infections (STIs) have been associated with longer hrHPV persistence in previous studies. Two studies of adolescent women in the United States showed significant positive associations between *Chlamydia trachomatis* and *Trichomonas vaginalis* and hrHPV persistence,[5,6] and two studies of adult women in Sweden and China showed that *Chlamydia trachomatis* and bacterial vaginosis, respectively, were significant risk factors for hrHPV persistence.[7,8] In light of these findings, management of STIs is a potential prevention strategy to reduce hrHPV persistence among women.

While this strategy might be effective among groups at relatively lower risk for hrHPV, few studies have explored the relationship between STIs and hrHPV persistence in high-risk groups, including female sex workers. Female sex workers (FSW) are at increased risk for acquiring hrHPV due to their higher number of sexual partners and frequency of sex acts. Prevalence studies among FSW indicate high hrHPV burden, sometimes affecting half or more of respondents.[9,10] In spite of being at high risk, only one published study has explored risk factors for hrHPV persistence among FSW[11], and to our knowledge none have focused on sub-Saharan Africa. In addition, few risk factor analyses have statistically quantified persistence of hrHPV infections using continuous time in number of days or months, rather than a number of time intervals.[12,13] Further, fully parametric methods for longitudinal data have not yet been implemented in the published literature to measure relative time to clearance of hrHPV infection, comparing individuals with and without given risk factors.

We present here results of a study to quantify the relative duration of hrHPV infection among FSW in Nairobi, Kenya with history of laboratory-confirmed infection with one or more of four STIs - *Chlamydia trachomatis* (CT), *Neisseria gonorrhea* (GC), *Trichomonas vaginalis* (TV), and *Mycoplasma genitalium* (MG) – using parametric regression methods for longitudinal data.

MATERIALS AND METHODS

Study population

Study procedures and data collection took place in the Korogocho clinic in Nairobi, Kenya. From August 2009 to March 2011, FSW attending the Korogocho clinic were invited to participate in the study during "baraza" public meetings, as previously described.[14] Women who had received hysterectomies or were in the second trimester of pregnancy or later were considered ineligible for the study. A total of 425 FSW ages 18–49 were approached to participate, and 350 provided written informed consent to enroll into the study. At screening, participants responded to a questionnaire, administered by a trained study nurse or counselor, to collect sociodemographic, reproductive, and sexual behavior data.

Sample collection and laboratory analyses

During a pelvic examination, a physician collected one cervical sample from each woman using a Cervex-Brush (Rovers Medical Devices, The Netherlands), which was then swirled in the PreservCyt medium (Hologic Corporation, Marlborough, MA) and later discarded. The physician then collected a second cervical sample for conventional Pap smear. Cervical samples were stored in liquid-based APTIMA assay media at the Korogocho clinic, and were transported the same day to the University of Nairobi research laboratory, which is approximately 15 kilometers from the clinical site. Cytological smears were evaluated at the University of Nairobi and classified according to the 2001 Bethesda System for cervical cytology. All smears were independently read by two cytopathologists blinded to hrHPV and STI testing results. For discrepant cases, the final diagnosis was made based on the consensus of the reviewing cytopathologists. Samples were processed the same day as collection for HIV testing, and were stored at 4° Celsius until shipment to the Hologic Corporation (formerly Gen-Probe) testing laboratory in San Diego, CA, USA for hrHPV and STI testing.

hrHPV and STI testing

Laboratory testing for hrHPV was conducted using the APTIMA HPV Assay (AHPV; Hologic Corporation, San Diego) which qualitatively detects E6/E7 mRNA of 14 hrHPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68).[15] Positive hrHPV samples were genotyped at the baseline visit (i.e. the first study visit for all participants) using the APTIMA HPV 16 18/45 Genotype Assay to determine the presence of hrHPV types 16 and 18/45; the assay does not detect any additional types and does not distinguish between types 18 and 45. hrHPV assay results were considered positive based on a signal-to-cutoff ratio of 0.5.[15]

Infection statuses for CT and GC were obtained with the APTIMA Combo 2 assay; for TV with the APTIMA TV assay; and for MG with the APTIMA research use only assay, using the same target capture, transcription-mediated amplification and hybridization steps as AHPV detection. All assays were performed according to the manufacturer's instructions, without knowledge of the Pap smear or other study results.

Measures

The study period comprised nine total clinic visits at approximately three-month intervals, with analysis beginning at a participant's first positive hrHPV test. Participants who entered the study with an existing hrHPV diagnosis were considered prevalent infections, whereas participants who were not infected until later in the study were considered incident hrHPV infections. Persistence of a hrHPV infection was quantified based on the number of consecutive positive hrHPV diagnoses at three-month study intervals. We counted the number of intervals from the first positive hrHPV test until at least one subsequent hrHPV test was negative, or until the participant was lost to follow-up. We computed a minimum and maximum duration of infection for each participant, accounting for unobserved time between clinic visits during which hrHPV infections could have occurred or cleared (Statistical Appendix). The difference in the clinic visit dates between the end and start of each interval was used to compute the minimum and maximum duration.

Only the first instance of continuous hrHPV infection per participant was considered for this analysis. Consecutive positive hrHPV tests were assumed to represent a persistent infection, as hrHPV type data were only available for the baseline samples. Duration of hrHPV infection was right censored at the time of last positive test for participants who a) missed two or more consecutive study visits following a positive hrHPV diagnosis (lost to follow up), or b) were still positive at the last study visit. If only a single visit was missed the missing hrHPV status was imputed using the last observed value for hrHPV status.

Statistical Analysis

Nonparametric survival curves were generated using the expectation-maximization iterative convex minorant (EM-ICM) algorithm, an extension of the standard Kaplan-Meier estimator for interval-censored data.[16] The generalized log-rank test statistic was used to compare the median duration of hrHPV infection between strata of STI and HIV infection status, cervical cytology, and sexual risk factors[16]. Parametric accelerated failure time (AFT) models were employed to estimate crude and adjusted time ratios (TR) among FSW who experienced hrHPV infection at any time during the observation period. The generalized gamma distribution was assumed to be the best fit. All analyses were performed using SAS version 9.4 (Cary, North Carolina).[17]

RESULTS

Participant health status and behavioral risk factors

Of the original 350 participants, 173 (49.4%) had a positive hrHPV result at least once over the course of the study, of which 103 (59.5%) had a prevalent hrHPV infection at baseline, and 70 (40.5%) acquired a hrHPV infection during follow-up. These 173 participants

comprised the final study sample. The median age of the participants in the sample was 27 years (range: 19 – 48). Over one-third (37.6%) of the participants reported participating in sex work for more than five years. Less than one-fourth (24.3%) of the participants reported using condoms consistently with their clients. The median number of clients per week was 12 (Appendix 2). The prevalence of each STI at baseline was as follows: CT – 6.4%; GC – 3.5%; MG – 16.8%; TV – 9.3% and HIV – 29.5% (Appendix 2).

Median follow-up time was 25.5 months (IQR: 8.5 – 27.4) among participants with prevalent hrHPV infections, and 26.6 months (IQR: 25.3 – 28.2) among participants with incident hrHPV infections. All participants had at least one missing visit of the total nine visits, requiring imputation of at least one missing hrHPV status. Among all infections, 99 (57.2%) experienced clearance of a hrHPV infection over follow-up, 46 were lost to follow up (26.6%), and 28 (16.2%) remained positive and were administratively censored after the ninth visit. Thirteen (12.6%) of the participants infected with hrHPV at baseline were infected with type 18/45; 14 (13.6%) were infected with type 16; 2 (1.9%) were infected with both 18/45 and 16; and 74 (71.8%) were infected with some other hrHPV type.

The median duration of hrHPV infection among all cases was 9.3 months (95% CI: 9.3, 11.5), with a range from 1.8 – 31.3 months (Table 1). Among those infected with type 16 at baseline, the median duration of infection was 23.6 months (95% CI: 5.7, ∞), and the median duration among those infected with type 18/45 was 11.5 months (95% CI: 5.2, 11.5); however this difference did not reach significance at the 0.05 alpha level (p=0.07). Median duration was significantly longer among participants infected with CT at baseline compared to those who were uninfected (19.4 months vs. 9.3 months, p=0.05) (Table 1, Figure 1a). FSW who reported 12 or more clients per week on average had a significantly longer median duration than those who had fewer than 12 (11.2 vs. 9.3, p=0.03). An increasing trend in median duration was also observed by levels of cervical cytology results (Normal=7.9; atypical squamous cells of undetermined significance (ASCUS), atypical glandular cells of undetermined significance (AGUS), or low-grade squamous intraepithelial lesions (LSIL)=11.5; HSIL=17.3, p=0.06). No significant differences were observed based on other STI infections, HIV status, age group, or sexual risk behaviors. The median duration of hrHPV infection was longer among participants infected with GC compared to those who were uninfected, but this finding did not reach statistical significance due in part to a small number of positive GC results (N=6).

Relative time to clearance of hrHPV infection

The median duration of hrHPV infection among participants infected with CT at baseline was almost twice that among participants who were uninfected at baseline (TR: 1.9, 95% CI: 1.1, 3.1) (Table 2). The positive association between CT and hrHPV persistence was slightly attenuated after adjusting for age and baseline HIV status, but remained statistically significant (TR: 1.7, 95% CI: 1.2, 2.6). Among participants who were infected with hrHPV at baseline, the duration of hrHPV infections was over three times as long (adjusted TR: 3.4, 95% CI: 2.4, 4.8) among participants who were co-infected with CT compared to those infected with hrHPV only (Table 3). No association was observed between CT at baseline and the duration of incident hrHPV infections. Restricting to participants with normal

cytology, the adjusted TR for the association between CT infection and time to clearance was 1.7 (95% CI: 1.1, 2.5). We could not restrict to participants with abnormal cytology due to limited sample size. A sensitivity analysis using a stricter definition of hrHPV clearance – two consecutive negative tests following a hrHPV infection – found a similar positive association between CT infection and hrHPV persistence. The estimate among prevalent hrHPV infections was not strongly affected quantitatively, however the estimate among incident infections achieved statistical significance in the sensitivity analysis (aTR: 3.7, 95% CI: 1.9, 7.1).

After adjusting for age and baseline HIV status, increasing severity of cytological changes were associated with longer time to clearance of hrHPV infection. Among FSW with ASCUS/AGUS/LSIL, time to clearance was 80% longer compared to FSW with normal cytology (adjusted TR: 1.8, 95% CI: 1.5, 2.2). Among FSW with HSIL, the time to clearance was twice as long compared to FSW with normal cytology (adjusted TR: 2.1, 95% CI: 1.6, 2.7) (Table 2) (Figure 1b–c).

DISCUSSION

Among a cohort of high-risk FSW in Nairobi, we found that women with laboratory-confirmed CT had a nearly two-fold duration of hrHPV infection. This relationship was not observed with respect to any other STI, nor with HIV in contrast with previous findings[18]. Positive associations between CT and HPV persistence was previously shown using polymerase chain reaction (PCR) to detect HPV DNA, and PCR, ligase chain reaction, strand displacement amplification, and microimmunofluorescence to detect CT DNA.[5,6] However, methodological limitations such as small sample size and self-reported STI history may have caused bias in previous works. The current study is the first to diagnose hrHPV infection among FSW using mRNA of the E6/E7 oncoproteins, and the first to use AFT models to estimate a relative duration of infection with hrHPV with respect to risk factors of interest, rather than defining persistence as presence of type-specific hrHPV at two consecutive points in time.

We measured the association between CT and hrHPV persistence, given that hrHPV persistence is consistently associated with higher risk of histological cervical intraepithelial neoplasia grade 2 or higher (CIN2+).[3] In contrast to our findings, a case-control study by Safaeian, et al found that baseline CT infection was not associated with prevalent or incident CIN2+ among women with hrHPV-positivity at baseline, but was positively associated with hrHPV acquisition.[19] This might indicate that shared sexual risk factors for acquiring CT and hrHPV, rather than an effect of CT on hrHPV persistence, explains the associations that have been observed between CT and cervical precancer and ICC. However, our findings are consistent with prior research on the potential etiological role of cervical inflammation in cervical cancer carcinogenesis, independent of hrHPV infection.[20,21] One biological explanation is that CT infection can lead to severe and chronic cervical inflammation through up-regulation of cytokines, proteins that trigger the immune response. In a South African study of HIV-infected women, CT was shown to produce greater concentrations than GC and TV of pro-inflammatory cytokines, including interleukins (IL), tumor necrosis factors (TNF), and macrophage inflammatory proteins (MIP).[22] Further, a study of 154

HPV-infected women from Hawaii found that persistent HPV infection was positively associated with elevated levels of MIP-1a and TNF, Type-1 cytokine IL-12, and regulatory cytokine IL-10.[23] The interaction between these inflammatory processes associated with both HPV and CT infections may cause epithelial damage to the cervix, leading to prolonged hrHPV infection and increasing the risk for developing precancerous cervical lesions.

While we observed an overall positive association between CT infection and hrHPV persistence, this association was strengthened when restricting to prevalent hrHPV cases (i.e. CT-hrHPV co-infection) and was not observed when restricting to incident hrHPV cases. This finding suggests that co-infection with CT is a more salient risk factor for hrHPV persistence than recent CT infection. This is a reasonable conclusion, given that all clinic attendees who test positive for STIs were treated and any inflammation caused by CT should have subsided following treatment. Women were treated for CT infection immediately after diagnosis, which typically occurred within a maximum of 1.5 months following the study visit, notably reducing the possibility of CT persistence between the three month study intervals. Due to a very small number of concurrent CT infections among incident hrHPV cases (n=4), we were not able to assess the effect of CT and hrHPV co-infection in this subset.

This study has several strengths. We used narrow and multiple follow-up intervals, allowing us to identify hrHPV infection and clearance more precisely than was possible in previous studies, many of which measured persistence based on the presence of hrHPV at two consecutive time points only, and collected data in intervals of six months to several years.[5,7,8,24–26,13,27–29]. Second, while parametric methods, notably logistic regression to estimate odds ratios, are popular for evaluating hrHPV persistence, AFT models to estimate time ratios had not been implemented to our knowledge in the published literature prior to this work. The fully-parametric AFT family of models is preferable to semiparametric longitudinal methods like Cox proportional hazards, notably by allowing more precise estimation of association measures for interval-censored data. Third, we were able to distinguish between prevalent and incident hrHPV infections acquired during the observation period. This allowed us to isolate the association of concurrent CT and hrHPV infection with hrHPV persistence as compared to the association of recent CT with hrHPV persistence. We found that individuals with prevalent and incident hrHPV infections had similar levels of behavioral and biological factors (Appendix 2). This finding supported combining incident and prevalent infections into a single sample, which has been done in previous studies of hrHPV persistence. Sensitivity analysis also showed that loss to follow-up had a minimal impact on the association between CT infection and hrHPV persistence and did not appreciably change the magnitude or interpretations of our findings (data not shown). Finally, the APTIMA hrHPV assay is highly sensitive and relatively more specific for the detection of HSIL than DNA-based methods. The APTIMA hrHPV assay detects HPV type 66, which was reclassified in 2009 by the International Agency for Research on Cancer as possibly carcinogenic, rather than carcinogenic.[30] However, HPV 66 is still included in other HPV tests, including the FDA-approved cobas® test by Roche.[31] Any loss in the specificity of the test by including this lower-risk type is minor.

Methodological limitations include a relatively small sample size and substantial loss to follow-up (26.6%) over nine visits. Additionally, AFT models do not allow for the analysis of time-varying covariates in order to reliably determine the impact of incident, recurrent, or unresolved STIs on hrHPV persistence. Finally, because genotype data for hrHPV types 16 and 18/45 were only available at the baseline visit, it was not possible to define persistence as the presence of the same hrHPV type in consecutive visits, as has been done in prior studies.[5,8,24,25,28,29] Because our follow-up intervals were short, the probability that consecutive infections were indeed of the same type is higher. However, this does not rule out the possibility of re-infection with the same or another hrHPV type in the space between intervals. Given the high rate of new partners in this population, new infections likely did occur with some frequency. Additionally, the evidence for type-specific immunity following hrHPV infection is not conclusive,[32,33] and there is evidence for a latency period of hrHPV infection during which it can lay dormant and reactivate in the future.[34–36] Still, the evidence is strong that repeated positive hrHPV diagnoses is an important risk factor for HSIL and ICC, regardless of whether this represents true persistence, reinfection, or reactivation of a latent infection. Incidentally, a study of high-risk adolescents in the United States found that re-detection of the same hrHPV DNA type by PCR after apparent clearance for six months or longer was positively associated with concurrent CT infection by PCR at the time of redetection of hrHPV DNA (hazard ratio: 3.14, 95% CI: 1.44, 6.86),[37] lending additional support to a relationship between CT and hrHPV persistence, whether overt or latent.

Our findings suggest that improved clinical management of CT may reduce the duration of hrHPV infections and risk for cervical precancer. These findings should be interpreted with caution, however, given that HPV persistence is an intermediate endpoint on the biological pathway between hrHPV infection and ICC risk, and is not equivalent to HSIL per se. Further research is needed on the impact of STI treatment on reducing hrHPV persistence and incidence of high grade lesions. Such research is feasible given that STI diagnosis and treatment can be achieved relatively cheaply and effectively, and is used to reduce secondary outcomes such as preterm birth and infertility.

The bivalent and quadrivalent HPV vaccines, which protect against hrHPV types 16 and 18, are the optimal preventive measures against hrHPV and cervical cancer, but are not yet widely available to the general public in Kenya due to cost and logistical restraints. Even if availability and acceptance of the vaccine were high, most FSW in our sample are beyond the approved age to receive either vaccine. Without a health care policy that implements widespread HPV vaccination of youth, hrHPV will continue to spread through high-risk populations in Kenya. Improving detection and treatment of STIs, particularly CT, might prove to be another prevention tool to reduce the burden of HSIL and associated ICC in resource-limited settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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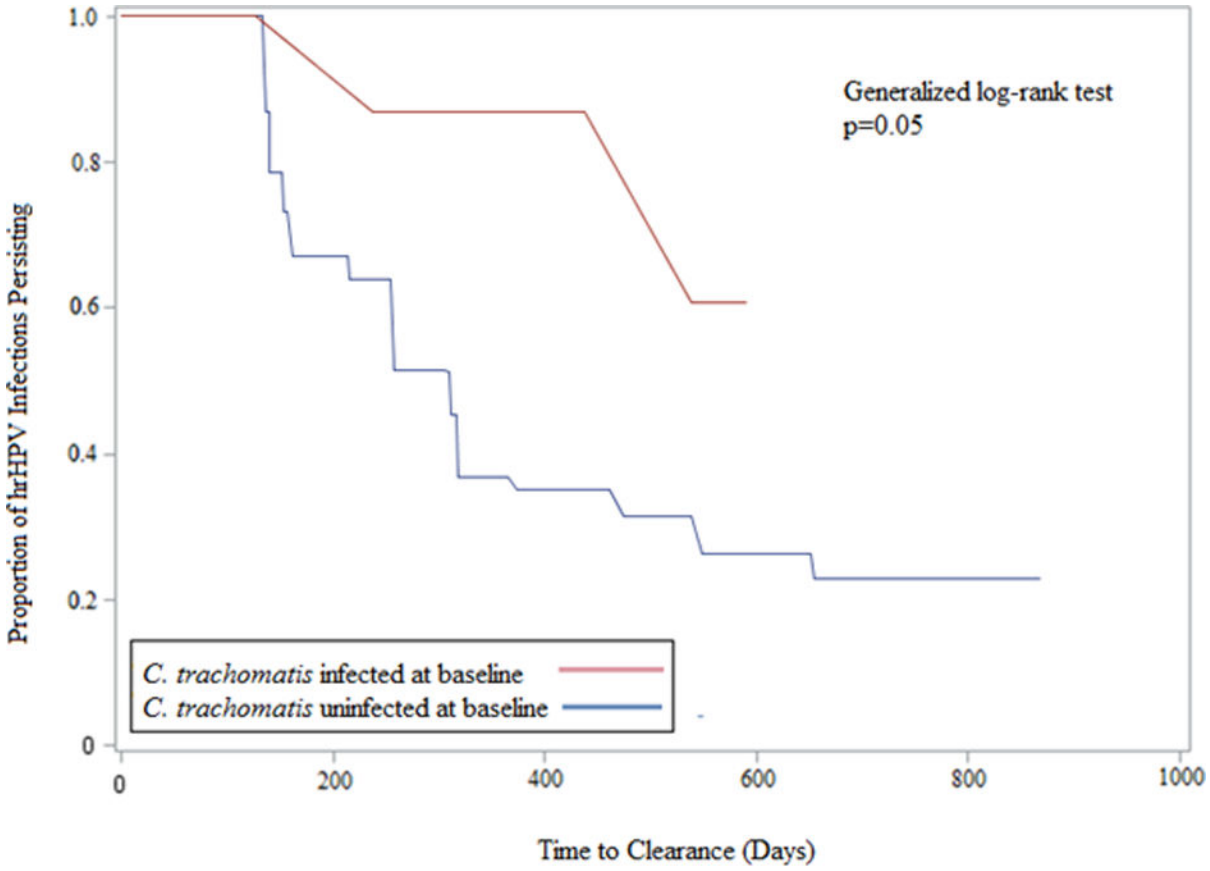

Figure 1.

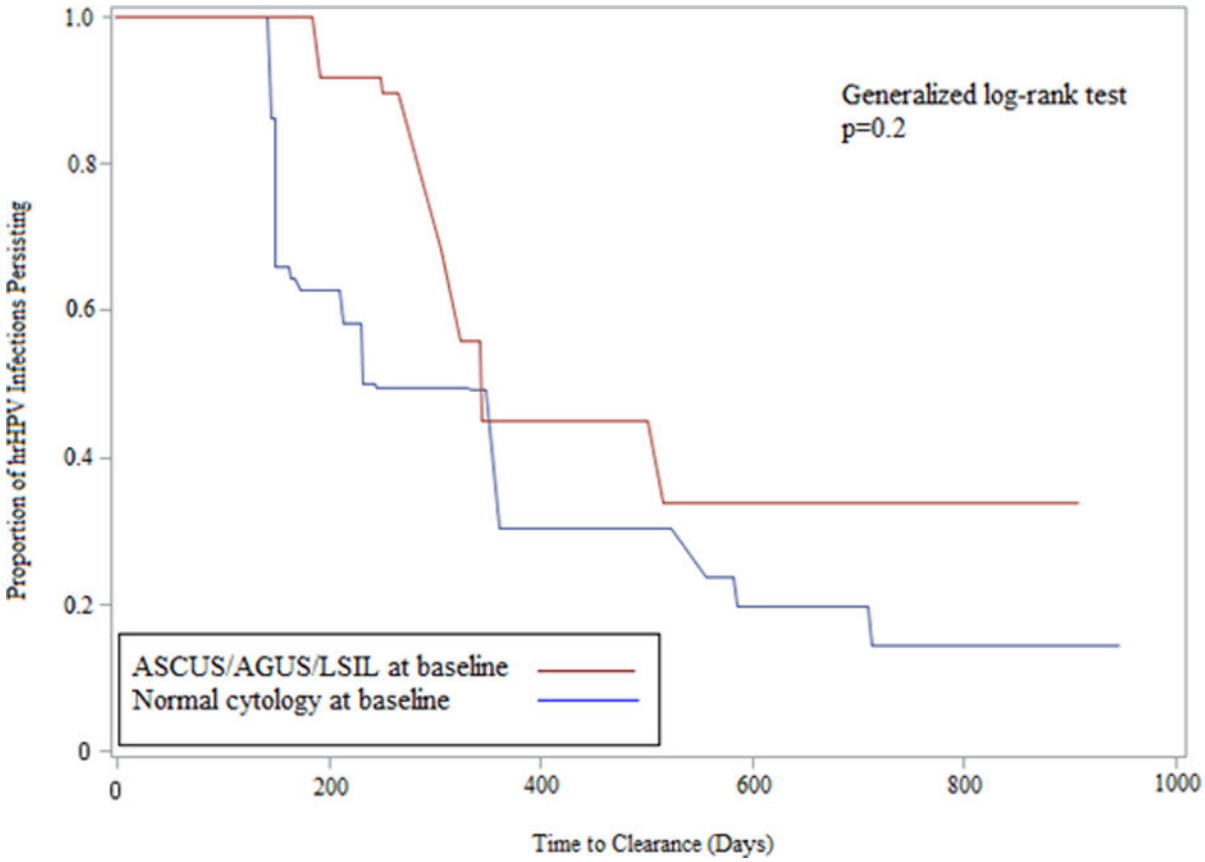

Figure 2.

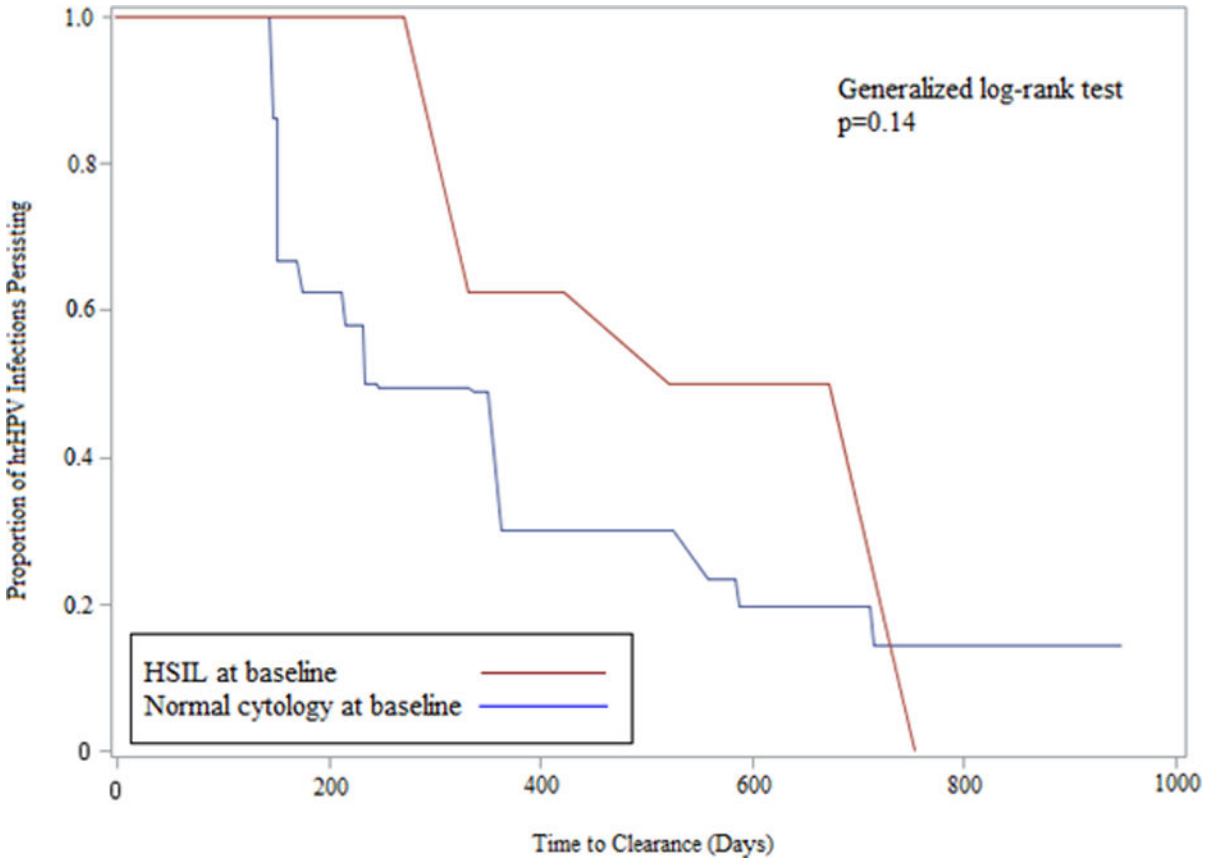

Figure 3.

Table 1

Median duration of hrHPV infection in months by baseline health status and sexual risk factors (N=173)

Variable	N (%)	Median duration (95% CI)	Generalized log-rank test statistic
Overall	173 (100%)	9.3 (9.3, 11.5)	–
CT[a,c]			
Negative	161 (93.1)	9.3 (9.3, 11.5)	
Positive	11 (6.4)	19.4 (8.6, ∞)	p=0.05
Missing	1 (0.6)	–	
GC[a]			
Negative	167 (96.5)	9.3 (9.3, 11.5)	p=0.16
Positive	6 (3.5)	20.0 (5.0, ∞)	
MG[a]			
Negative	157 (90.8)	10.3 (9.3, 11.3)	p=0.23
Positive	16 (9.2)	7.8 (5.6, 12.1)	
TV[a]			
Negative	144 (83.2)	9.3 (9.3, 11.5)	p=0.54
Positive	29 (16.8)	10.2 (5.7, 19.4)	
Cytological Results[b]			
Normal	131 (75.7)	7.9 (7.2, 12.1)	
ASCUS/AGUS/LSIL	29 (16.8)	11.5 (10.2, ∞)	p=0.06
HSIL	13 (7.51)	17.3 (11.0, 24.8)	
HIV status			
Negative	122 (70.5)	11.4 (10.2, 11.5)	p=0.76
Positive	51 (29.5)	9.3 (5.7, 23.6)	
Age (years)			
18–24	54 (31.2)	9.4 (9.4, 11.5)	
25–29	57 (32.9)	11.5 (8.4, 17.2)	p=0.79
30–34	32 (18.5)	10.7 (5.1, 10.8)	
35+	30 (17.3)	9.6 (9.6, 16.1)	
Duration of sex work			
More than 5 years	65 (37.6)	11.5 (9.3, 11.5)	p=0.13
5 years or fewer	108 (62.4)	8.8 (5.9, 8.8)	
Consistent condom use			
Half the time or less	50 (28.9)	9.6 (5.9, 17.3)	
Most of the time	81 (46.8)	9.3 (9.1, 11.5)	p=0.97
Always	42 (24.3)	13.2 (5.0, 17.3)	
Average number of clients per week			
12 or more	86 (49.7)	11.2 (9.1, 17.2)	p=0.03
Fewer than 12	87 (50.3)	9.3 (9.3, 10.3)	

[a] CT=chlamydia trachomatis; GC=neisseria gonorrhea; MG=mycoplasma genitalium; TV=trichomonas vaginalis; HIV=human immunodeficiency virus

[b] ASCUS=atypical squamous cells of undetermined significance; AGUS=atypical glandular cells of undetermined significance; LSIL=low-grade squamous intraepithelial lesions; HSIL=high-grade squamous intraepithelial lesions

[c] Median time to clearance was unavailable if fewer than 50% in the stratum achieved clearance. Instead, the 25th percentile is used.

Table 2

Crude and adjusted time ratios (TR)[a] for duration of (hrHPV) infection by baseline health status and sexual risk factors (N=173)

Variable	N (%)	Crude TR (95% CI)	Adjusted TR[e] (95% CI)
CT[c]			
Negative	161 (93.1)	1.0 (ref)	1.0 (ref)
Positive	11[b] (6.4)	**1.9 (1.1, 3.1)**	**1.7 (1.2, 2.6)**
GC[c]			
Negative	167 (96.5)	1.0 (ref)	
Positive	6 (3.5)	0.8 (0.5, 1.3)	
TV[c]			
Negative	157 (90.8)	1.0 (ref)	
Positive	16 (9.2)	1.0 (0.7, 1.4)	
MG[c]			
Negative	144 (83.2)	1.0 (ref)	
Positive	29 (16.8)	0.9 (0.7, 1.2)	
Cytological Results[d]			
Normal	131 (75.7)	1.0 (ref)	1.0 (ref)
ASCUS/AGUS/LSIL	29 (16.8)	**1.6 (1.2, 2.3)**	**1.8 (1.5, 2.2)**
HSIL	13 (7.51)	**2.2 (1.7, 2.9)**	**2.1 (1.6, 2.7)**
HIV status[c]			
Negative	122 (70.5)	1.0 (ref)	
Positive	51 (29.5)	0.8 (0.6, 1.0)	
Age			
18–24	54 (31.2)	1.0 (ref)	
25–29	57 (32.9)	1.0 (0.8, 1.2)	
30–34	32 (18.5)	1.2 (0.6, 1.1)	
35+	30 (17.3)	1.0 (0.8, 1.3)	
Duration of sex work			
More than 5 years	65 (37.6)	1.0 (ref)	
5 years or fewer	108 (62.4)	0.8 (0.7, 1.0)	
Consistent condom use			
Half the time or less	50 (28.9)	1.0 (ref)	
Most of the time	81 (46.8)	1.1 (0.8, 1.3)	
Always	42 (24.3)	0.9 (0.6, 1.2)	
Average number of clients per week			
12 or more	86 (49.7)	1.0 (ref)	
Fewer than 12	87 (50.3)	1.0 (0.8, 1.2)	

[a] Time ratio reflects the relative duration of hrHPV infection, comparing those with a given characteristic to those without.

[b] 1 observation missing

[c] CT=chlamydia trachomatis; GC=neisseria gonorrhea; MG=mycoplasma genitalium; TV=trichomonas vaginalis; HIV=human immunodeficiency virus

[d] ASCUS=atypical squamous cells of undetermined significance; AGUS=atypical glandular cells of undetermined significance; LSIL=low-grade squamous intraepithelial lesions; HSIL=high-grade squamous intraepithelial lesions

[e] Adjusted for baseline HIV status and age

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Table 3

Crude and adjusted time ratios (TR)[a] for duration of high-risk HPV (hrHPV) infection by baseline STI status (N=173)

	Prevalent HPV Infections (n=103)[b]			Incident HPV Infections (n=70)[b]		
STI Status	**N (%)**	**Crude TR (95% CI)**	**Adjusted TR[e] (95%CI)**	**N (%)**	**Crude TR (95% CI)**	**Adjusted TR[e] (95%CI)**
CT[c]						
Negative	98 (95.1)	1.0 (ref) **3.7**	1.0 (ref) **3.4**	63 (90.0)	1.0 (ref) 1.01	
Positive	5 (4.9)	**(2.6, 5.3)**	**(2.4, 4.8)**	6[d] (8.6)	(0.4, 2.5)	
GC[c]						
Negative	99 (96.1)	1.0 (ref) 0.8		68 (97.1)	1.0 (ref) **2.4**	**1.0 (ref)** **2.4**
Positive	4 (3.9)	(0.5, 1.3)		2 (2.9)	**(1.5, 3.7)**	**(1.5, 4.0)**
TV[c]						
Negative	92 (89.3)	1.0 (ref) 0.9		65 (92.9)	1.0 (ref) 1.2	
Positive	11 (10.7)	(0.6, 1.3)		5 (7.1)	(0.7, 2.0)	
MG[c]						
Negative	86 (83.5)	1.0 (ref) 1		58 (82.9)	1.0 (ref) 0.8	
Positive	17 (16.5)	(0.6, 1.7)		12 (17.1)	(0.5, 1.2)	

[a] Time ratio reflects the relative duration of hrHPV infection, comparing those who are infected with a given STI to those who are uninfected

[b] Prevalent infections are among participants who were HPV-infected at enrollment per APTIMA HPV Assay of a physician-collected cervical specimen. Incident infections are among participants who were HPV-uninfected at enrollment, but became infected over the follow-up period per APTIMA HPV Assay of a physician-collected cervical specimen

[c] CT=chlamydia trachomatis; GC=neisseria gonorrhea; MG=mycoplasma genitalium; TV=trichomonas vaginalis; HIV=human immunodeficiency virus

[d] 1 observation missing

[e] Adjusted for baseline HIV status and age