Vaccine-Relevant Human Papillomavirus (HPV) Infections and Future Acquisition of High-Risk HPV Types in Men

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Background. Little is known about type-specific associations between prevalent human papillomavirus (HPV) infections and risk of acquiring other HPV types in men. Data on natural clustering of HPV types are needed as a prevaccine distribution to which postvaccine data can be compared.

Methods. Using data from a randomized controlled trial of male circumcision in Kisumu, Kenya, adjusted mean survival ratios were estimated for acquisition of any-HPV, high-risk (HR) HPV, and individual HR-HPV types among men uninfected as compared to those infected with vaccine-relevant HPV types 16, 18, 31, 45, 6, or 11 at baseline.

Results. Among 1097 human immunodeficiency virus–negative, uncircumcised men, 2303 incident HPV infections were detected over 2534 person-years of follow-up. Although acquisition of individual HR-HPV types varied by baseline HPV type, there was no clear evidence of shorter times to acquisition among men without vaccine-relevant HPV-16, -18, -31, -45, -6, or -11 infections at baseline, as compared to men who did have these infections at baseline.

Conclusions. These prospective data on combinations of HPV infections over time do not suggest the potential for postvaccination HPV type replacement. Future surveillance studies are needed to definitely determine whether elimination of HPV types by vaccination will alter the HPV type distribution in the population.

Human papillomavirus (HPV) infection is the primary cause of cervical cancer in women [1, 2]. Other genital cancers, including vaginal, vulvar, anal, and penile carcinoma are also caused by HPV infection. Multiple HPV types have been detected in 20%–73% of HPV-infected males [3–9] and are important for the risk of transmission to female sexual partners and development of anogenital cancers. With the recent approval of prophylactic HPV vaccination of young men [10], data are needed to understand if patterns of HPV acquisition differ among men with specific HPV type infections as compared to men without these HPV infections. The effect of current vaccine-relevant HPV infections on the subsequent acquisition of different HPV types could impact the long-term potential for HPV type replacement following population-based HPV vaccination [11, 12].

Previous studies have shown that infection with multiple HPV types occurs more often than expected if the infections were independent [13–17]. Women with HPV infection at baseline are more likely to acquire additional HPV types during follow-up than those uninfected [5, 18–21]. In analyses limited to 5 HPV types, DNA detection of HPV-16, -18, -31, -45 or -6 did not predict acquisition of any of the other 4 specific HPV types among female university students from the United States [21]. In contrast, among cytologically normal women from Colombia, incident infection with HPV-16 and HPV-18 was associated with higher odds of acquiring

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HPV-58, but not 5 other HPV types [11]. In a population of cytologically normal women from the United States [18] and in the ASCUS/LSIL Triage Study [19], all HPV infections, regardless of type, were associated with higher acquisition rates of other HPV types, as compared to being uninfected, likely due to a common mode of transmission, host immunity, or shared risk factors.

While there are differences in the natural history of type-specific HPV infections between women and men [22, 23], no prospective studies have examined the interactions between specific HPV types over time in men. Therefore, using data from a longitudinal cohort of young uncircumcised men from Kisumu, Kenya, we compared time to acquisition of overall HPV, high-risk (HR) HPV, and 14 individual HR-HPV types among men DNA positive as compared to DNA negative for vaccine-relevant HPV types 16, 18, 31, 45, 6, or 11 at baseline.

METHODS

Study Population and Design

A randomized controlled trial (RCT) was conducted in Kisumu, Kenya, from 2002 to 2006 to determine the effectiveness of male circumcision in reducing the incidence of human immunodeficiency virus (HIV) infection [24]. A cohort study on the natural history of HPV infections in men was nested in the RCT [25, 26]. Briefly, eligible males were between 18 and 24 years old, uncircumcised, HIV seronegative, and sexually active. Of the 2784 men enrolled in the RCT, 2228 were enrolled in the nested HPV study. Of the 1102 men randomized to the delayed circumcision (control) arm, the present study includes 1097 men who had HPV DNA results at baseline and ≥1 follow-up visit. This analysis focused on uncircumcised men only because male circumcision has been shown to affect HPV acquisition and many men may remain uncircumcised due to lack of access or personal beliefs [27, 28].

Study visits were conducted at baseline and every 6 months for 24 months of follow-up. At baseline and each biannual visit, trained male interviewers administered a standardized questionnaire on sociodemographic characteristics, sexual behavior, and other medical conditions. A physician or clinical officer conducted a physical examination during which a urine sample was collected for polymerase chain reaction (PCR) detection of *Chlamydia trachomatis* (Roche Diagnostics). For HPV DNA detection, penile exfoliated cells were collected separately from 2 anatomical sites using prewetted Dacron swabs: (1) shaft and external foreskin and (2) glans, coronal sulcus, and inner foreskin [26]. All participants provided informed consent and all study protocols were approved by institutional review boards at each collaborating institution.

Detection of HPV DNA

DNA was isolated from penile cell samples and the presence of human DNA was evaluated by β-globin–specific PCR [29, 30]. HPV DNA was assessed by GP5+/6+ PCR, followed by hybridization of PCR products using an enzyme immunoassay readout with 2 HPV oligoprobe cocktail probes that detect 44 HPV types. Subsequent HPV genotyping was performed by reverse line blot hybridization of the PCR products, as described previously [29, 30]. HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 were classified as HR-HPV types, and the other 30 HPV types were categorized as low-risk HPV. HPV infections detected by PCR but not by reverse line blot genotyping were designated as HPV X and were not included in either the high- or low-risk categories. HPV detection was performed on the shaft and glans samples separately. We present here the pooled HPV DNA results from both anatomical sites combined.

Statistical Analysis

HPV types 16, 18, 6, and 11 were chosen as baseline types of interest due to their inclusion in current generation HPV prophylactic vaccines [31, 32]. Given the relatively high prevalence of HPV-45 in adenocarcinoma and the potential for HPV cross-protection against HPV-31 [33], we also investigated associations between HPV-31 and HPV-45 and future HPV acquisition. The study outcomes were time to acquisition of any other HPV types except the baseline type of interest, any other HR-HPV infection, and acquisition of each of the other 13 individual HR-HPV types. For all analyses, type-specific HPV acquisition was defined as the detection of a new HPV genotype at the current visit that was not detected at any of the previous study visits.

Time to first infection for each HPV type was analyzed using interval-censored survival methods, because acquisition events were only known to have occurred between the last HPV-negative visit and the first HPV-positive visit [34]. For each HPV type where an acquisition was not observed, the data were right censored at the final study visit. If men crossed-over to the circumcision arm during the study period before acquiring a type-specific infection (n = 51), they were right censored at their last visit with HPV DNA results prior to circumcision. If HPV DNA results were missing for the visit(s) before the first HPV-positive visit, the acquisition interval spanned from the last nonmissing HPV-negative visit to the first HPV-positive visit. If a result was missing between 2 HPV-negative visits, then the missing value was assumed to be HPV negative. When this assumption was evaluated by changing the missing values from HPV negative to HPV positive, there was a minimal effect on the adjusted mean survival ratios (aMSRs) for HPV acquisition (data not shown).

Unadjusted survival curves were used to graphically display the pattern of HPV acquisition, stratified by HPV-16, -18, -31, -45, -6, and -11 DNA status at baseline. The probability of acquiring an HPV infection as a function of time was estimated using the generalized Kaplan-Meier estimator [35, 36],

which allows for arbitrarily (interval) censored data via the published SAS macro %ICE [37]. Differences between groups were assessed using a generalization of the log-rank test for interval-censored data [38].

Parametric frailty survival models, allowing for the correlation between HPV types among men with multiple infections and for interval-censored data [34], were used to estimate the associations between type-specific infections at baseline and acquisition of any-HPV and HR-HPV infections. To estimate the association between vaccine-relevant HPV infections at baseline and acquisition of each individual HR-HPV type, parametric survival models without the random effects frailty term were used. Log-logistic, log-normal, and Weibull parametric accelerated failure time models were considered [39]. Model diagnostics suggested that the log-logistic distribution provided the best fit to the data. The models were parameterized such that the aMSR equaled the mean time until type-specific HPV acquisition in men without a specific vaccine-relevant HPV type at baseline divided by the mean time to acquisition in men with that HPV type at baseline. Estimated aMSRs <1.0 indicate that men without the vaccine-relevant HPV type infection at baseline acquire other HPV types earlier on average and suggest the potential for type replacement. An aMSR >1.0 indicates that men without a vaccine relevant type at baseline acquire other HPV types later than men with that type at baseline.

All models were adjusted for potential confounding variables, including baseline age (centered at 20 years), number of sexual partners (6 months prior to baseline), consistent condom use (in 6 months prior to baseline), bathing frequency, and *C. trachomatis* infection, which were previously shown to be associated with multiple HPV infections in this cohort [40]. Interpretation of study results were based on patterns of HPV acquisition, defined by the magnitude and precision of the estimates, rather than on statistical significance alone.

RESULTS

The median age of the 1097 men was 20 years (interquartile range [IQR], 19–22 years) (Table 1). Most men were not married (94%) and were not earning an income (52%), with a median of 11 years of education (IQR, 8–12 years) (Table 1). The median age at sexual debut was 16 years (IQR, 14–17 years), and over half of men reported 0 or 1 sexual partners in the previous 6 months (57%). Consistent condom use in the previous 6 months was reported by roughly a quarter of men (23%) and *C. trachomatis* infection was detected in 4% of men at baseline. There was a median of 184 days (IQR, 183–187 days) between study visits.

At baseline, 50% of men were HPV infected, with multiple infections (n = 314; 29%) detected more often than single HPV infections (n = 231; 21%; $P < .01$) (Table 2). The prevalence of vaccine-relevant types at baseline ranged from 9% for HPV-16 (n = 103) to 2% for HPV-11 (n = 21). During follow-up, the prevalence of HPV ranged from 49% (18 months) to 41% (24 months), and the median number of types among men with detectable HPV was 2 (range, 1–15). A total of 132 men (12%) had no detectable HPV at all 5 study visits. β-globin was detected in 73% of all penile samples (range per visit, 63%–85%). The prevalence of HPV among β-globin–positive samples at baseline (52%) was very similar to the prevalence in the entire cohort (50%) and results of parametric frailty models were similar when restricting only to men with β-globin–positive samples (online Supplementary Appendix Table 1).

A total of 2303 HPV infections were acquired over study follow-up, of which 1147 (50%) were HR-HPV types (Table 3). The most commonly acquired types were HPV-16 (n = 185), HPV-56 (n = 122), HPV-35 (n = 109), HPV-42 (n = 102), HPV-67 (n = 99), and HPV-6 (n = 98). For the fitted

Table 1. Baseline Characteristics of the Uncircumcised, HIV-Negative Male Study Population (N = 1097)

	Study Population[a] N (%) or Median (IQR)
Age in years	20 (19–22)
Marital status	
Not married	1025 (93.8)
Married	67 (6.2)
Earning an income	
No	570 (52.2)
Yes	523 (47.9)
Years of education	11 (8–12)
Bathing frequency	
Less than daily	22 (2.0)
Daily	1062 (98.0)
Age at sexual debut in years	16 (14–17)
Number of sexual partners (6 mo)	
0–1 Partners	618 (56.5)
≥2 partners	475 (43.5)
Condom use (6 mo)	
Not always	751 (76.8)
Always[b]	227 (23.2)
C. trachomatis infection	
No	1041 (96.1)
Yes	42 (3.9)
Length of testing interval (days)	184 (183–187)
Number of visits per person	5 (4–5)

Abbreviations: N, number; %, percentage; IQR, interquartile range.

[a] Missing: marital status (n = 5), employment status (n = 4), bathing frequency (n = 13), age at sexual debut (n = 4), number of partners (n = 4), condom use (n = 119), *C. trachomatis* (n = 14).

[b] Condom use "always" category includes men reporting no sex in last 6 months (n = 19).

Table 2. Prevalence of HPV Infection in 1097 Uncircumcised Males Over 24 Months of Follow-up

	Visit 1 (baseline) N (%)	Visit 2 (6 mo) N (%)	Visit 3 (12 mo) N (%)	Visit 4 (18 mo) N (%)	Visit 5 (24 mo) N (%)
HPV DNA positive	545 (49.7)	440 (45.3)	479 (48.4)	474 (49.1)	378 (41.0)
Single HPV infection	231 (21.1)	210 (21.6)	226 (22.8)	222 (23.0)	173 (18.8)
Multiple HPV infections	314 (28.6)	230 (23.7)	253 (25.6)	252 (26.1)	205 (22.2)
Number of HPV types[a]	2 (1–11)	2 (1–15)	2 (1–10)	2 (1–8)	2 (1–8)
HPV-16	103 (9.4)	91 (9.4)	78 (7.9)	58 (6.0)	77 (8.4)
HPV-18	37 (3.4)	34 (3.5)	31 (3.1)	42 (4.4)	29 (3.2)
HPV-31	40 (3.7)	24 (2.5)	28 (2.8)	19 (2.0)	18 (2.0)
HPV-45	50 (5.6)	19 (2.0)	25 (2.5)	28 (2.9)	20 (2.2)
HPV-6	38 (3.5)	33 (3.4)	37 (3.7)	51 (5.3)	31 (3.4)
HPV-11	21 (1.9)	16 (1.7)	22 (2.2)	21 (2.2)	10 (1.1)
Missing HPV results[b]		125	107	132	175

Abbreviations: N, number; %, percentage; HPV, human papillomavirus.

[a] Median (range) among men with detectable HPV infection.

[b] Includes missed study visits and samples that were inadequate for HPV testing.

parametric frailty models, the mean times to acquisition of any-other HPV infection were about 2 times longer among men without HPV-18 (aMSR, 2.2; 95% confidence interval [CI], 1.4–3.3) or HPV-45 (aMSR, 2.1; 1.5–2.9) than in men with that type at baseline. Infection with HPV-16 at baseline was not associated with time to any-HPV (aMSR, 1.2; 95% CI, .9–1.6) and HR-HPV (aMSR, 1.1; .8–1.5) acquisition. For the group of types included in the HPV vaccines (Table 3), there was a longer time to any-HPV (aMSR, 1.5; 1.1–1.9) and HR-HPV (aMSR, 1.3; 1.0–1.7) acquisition among men negative for both HPV-16 and HPV-18 at baseline than in men positive for HPV-16 and/or HPV-18. Similar aMSRs were observed when comparing men without any HPV-16, -18, -6, or -11 at baseline to men with HPV-16, -18, -6, and/or -11 infection at baseline.

Table 3. Associations Between Type-Specific HPV Infections at Baseline and Future Acquisition of Any Other HPV (n = 2303 infections) and HR-HPV (n = 1147 infections) Over 24 Months of Follow-up

	HPV Acquisition	
	Any-HPV[a]	HR-HPV[b]
Baseline HPV	aMSR (95% CI)[c]	aMSR (95% CI)[c]
HPV-16 (n = 103)	1.2 (.9, 1.6)	1.1 (.8, 1.5)
HPV-18 (n = 37)	2.2 (1.4, 3.3)	1.7 (1.0, 2.7)
HPV-31 (n = 40)	1.5 (1.0, 2.3)	1.6 (1.0, 2.5)
HPV-45 (n = 50)	2.1 (1.5, 2.9)	1.8 (1.3, 2.7)
HPV-6 (n = 38)	1.2 (.8, 1.9)	1.1 (.7, 1.8)
HPV-11 (n = 21)	1.6 (.9, 2.7)	1.5 (.9, 2.7)
HPV-16, 18 (n = 136)[d]	1.5 (1.1, 1.9)	1.3 (1.0, 1.7)
HPV-6, 11 (n = 58)[e]	1.4 (1.0, 1.9)	1.3 (.9, 1.9)
HPV-16, 18, 6, 11 (n = 178)[f]	1.4 (1.1, 1.8)	1.3 (1.0, 1.7)

Abbreviations: HPV, human papillomavirus; HR, high-risk; aMSR, adjusted mean survival ratio; CI, confidence interval.

[a] Acquisition of all other HPV type infections except exposure HPV type: number of HPV-16 acquisition events = 185; HPV-18 = 94; HPV-31 = 57; HPV-45 = 70; HPV-6 = 98; HPV-11 = 51.

[b] All other HR-HPV types except exposure HPV type.

[c] Parametric frailty models adjusted for age(centered at 20 years), bathing frequency, number of sexual partners (in 6 months prior to baseline), consistent condom use (in 6 months prior to baseline), current *C. trachomatis* infection.

[d] Index group HPV-16 and -18 negative vs referent group HPV-16 and/or -18 positive.

[e] Index group HPV-6 and -11 negative vs referent group HPV-6 and/or -11 positive.

[f] Index group HPV-16, -18, -6, and -11 negative vs referent group HPV-16, -18, -6, and/or -11 positive.

Patterns of HR-HPV acquisition presented in the unadjusted survival curve estimates (Figure 1) are consistent with the results from the parametric frailty models (Table 3). Over study follow-up, there was no difference in HR-HPV acquisition between men uninfected with HPV-16 or HPV-6 at baseline and infected men, whereas men without HPV-31 or -11 had slightly lower probabilities of HR-HPV acquisition than infected men. Baseline infection with HPV-18 and HPV-45 resulted in consistently higher probabilities of acquiring other HR-HPV types over 24 months of study follow-up.

None of the 13 individual HR-HPV types were acquired earlier in men without HPV-16 at baseline than in men infected with HPV-16 at baseline (Table 4). Men who were HPV-16 uninfected at baseline acquired HPV-31 (aMSR, 2.1; 95% CI, 1.0–4.6) and HPV-58 (aMSR, 3.7; 95% CI, 1.8–7.4) later, on average, than men with HPV-16. Among men without HPV-18 at baseline, compared to HPV-18–infected men, time to acquisition of each of the individual HR-HPV types appeared to be equal or slightly longer, except for HPV-31 (aMSR, 0.7; 95% CI, .1–4.3). Similarly, for HPV-31 DNA status at baseline, aMSRs ranged from 0.5 (95% CI, .1–2.6) for acquisition of

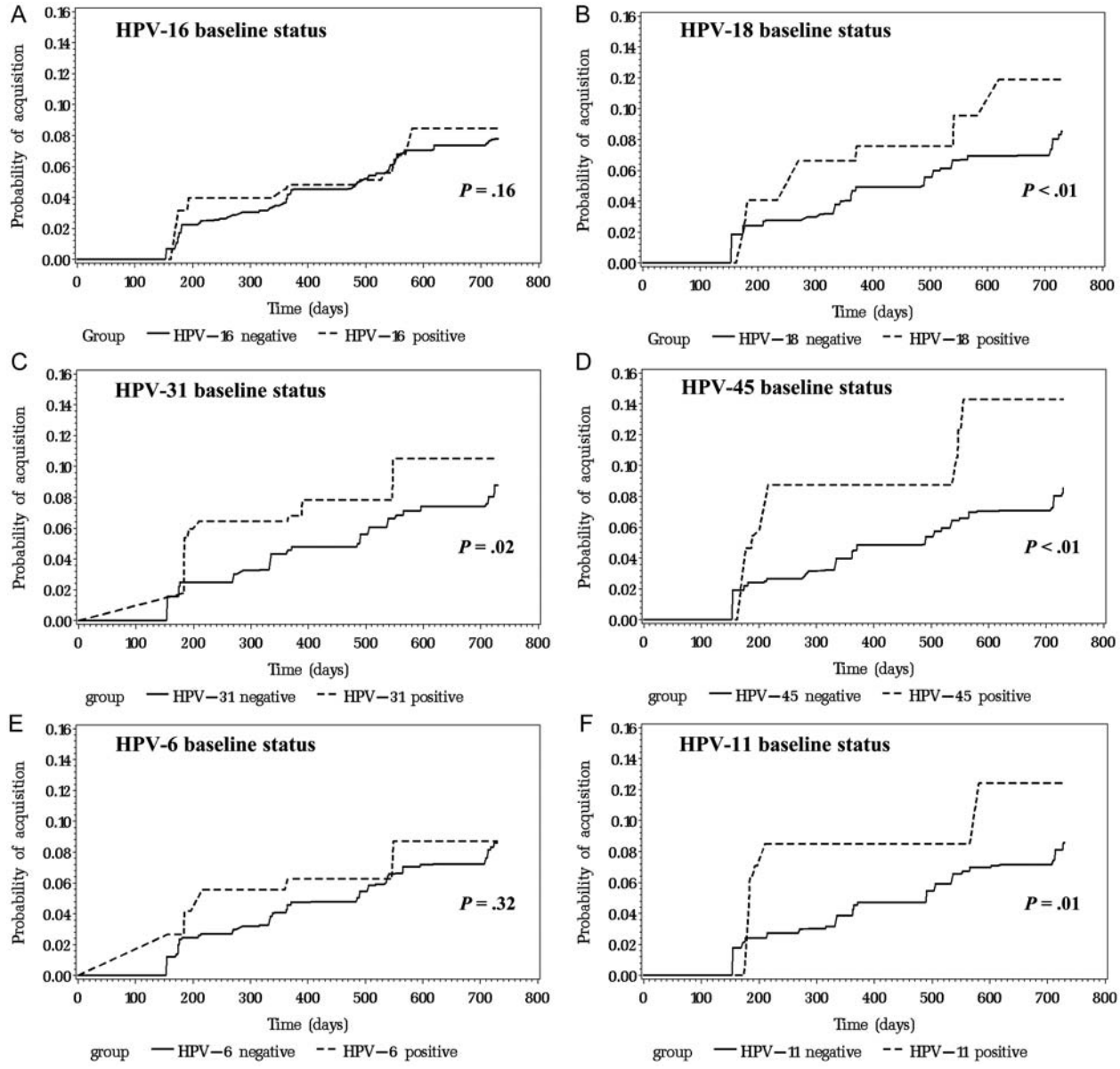

Figure 1. Estimates of the cumulative probability of acquisition of other high-risk human papillomavirus (HPV) types over 24 months by baseline infection status. *A,* HPV-16 DNA negative (*solid line*) versus positive (*dashed line)* at baseline. *B,* HPV-18 DNA negative versus positive. *C,* HPV-31 DNA negative versus positive. *D,* HPV-45 DNA negative versus positive. *E,* HPV-6 DNA negative versus positive. *F,* HPV-11 DNA negative versus positive.

HPV-45 to 2.3 (95% CI, .8–6.3) for acquisition of HPV-66, and all CIs included 1.0. Men without a baseline HPV-45 infection acquired HPV-31 (aMSR, 3.0; 95% CIs, 1.1–7.6), HPV-39 (aMSR, 3.7; 95% CI, 1.7–7.8), HPV-66 (aMSR, 3.4; 95% CI, 1.4–8.2), and HPV-51(aMSR, 2.2; 1.0–4.9) later, on average, than men with HPV-45 at baseline. Baseline negativity to low-risk HPV-6 or HPV-11 was generally associated with a similar or longer time to acquisition of the 14 individual HR-HPV types as compared to men infected with HPV-6 or HPV-11 at baseline. The aMSR for acquisition of HPV-35, comparing men without and those with HPV-11 at baseline, was the largest of the type-specific point estimates (aMSR, 5.8; 95% CI, 1.8–18.7). Mean survival ratios did not indicate that men without HPV-6 or HPV-11 at baseline acquired other HR-HPV infections earlier than men who were infected with HPV-6 or HPV-11 at baseline.

A comparison of average time until type-specific HPV acquisition between men with no vaccine-included HPV types and men with any of the 2 or 4 vaccine-included HPV types is presented in Table 5. The results of this analysis indicate that the times to acquisition of most non–vaccine-preventable HR-HPV types are similar or slightly longer among men negative

Table 4. Associations Between Type-Specific HPV Infections at Baseline and Future Acquisition of Individual HR-HPV Types

	Baseline HPV Infection					
HPV Acquisition	HPV-16 (n = 103) aMSR (95% CI)[a]	HPV-18 (n = 37) aMSR (95% CI)[a]	HPV-31 (n = 40) aMSR (95% CI)[a]	HPV-45 (n = 50) aMSR (95% CI)[a]	HPV-6 (n = 38) aMSR (95% CI)[a]	HPV-11 (n = 21) aMSR (95% CI)[a]
Clade A9						
HPV-16 (n = 185)	N/A	1.5 (.6, 3.9)	1.4 (.5, 3.5)	1.3 (.6, 2.8)	1.2 (.4, 3.1)	3.0 (.9, 9.9)
HPV-31 (n = 57)	2.1 (1.0, 4.6)	0.7 (.1, 4.3)	N/A	3.0 (1.1, 7.6)	1.8 (.5, 6.3)	3.0 (.8, 10.7)
HPV-33 (n = 72)	1.2 (.7, 2.2)	1.9 (.8, 4.4)	0.9 (.3, 2.6)	1.6 (.8, 3.3)	0.9 (.3, 2.7)	1.3 (.4, 4.2)
HPV-35 (n = 109)	1.0 (.4, 2.2)	2.2 (.7, 6.8)	1.2 (.4, 3.9)	1.1 (.4, 3.1)	1.1 (.3, 3.6)	5.8 (1.8, 18.7)
HPV-52 (n = 64)	0.7 (.3, 1.9)	2.0 (.6, 6.4)	2.2 (.8, 6.1)	1.5 (.6, 4.2)	2.3 (.8, 6.5)	N/E
HPV-58 (n = 77)	3.7 (1.8, 7.4)	1.9 (.6, 6.2)	2.2 (.7, 6.8)	2.2 (.8, 6.0)	1.5 (.4, 4.9)	2.1 (.5, 8.5)
Clade A7						
HPV-18 (n = 94)	1.0 (.5, 2.0)	N/A	1.3 (.4, 3.8)	0.7 (.2, 2.3)	1.4 (.5, 3.8)	1.0 (.3, 3.9)
HPV-39 (n = 52)	0.7 (.3, 1.8)	1.2 (.4, 4.2)	1.1 (.3, 3.7)	3.7 (1.7, 7.8)	0.5 (.1, 3.0)	N/E
HPV-45 (n = 70)	0.5 (.2, 1.4)	1.0 (.3, 3.4)	0.5 (.1, 2.6)	N/A	0.8 (.2, 3.0)	1.5 (.4, 5.4)
HPV-59 (n = 58)	0.4 (.1, 1.5)	1.5 (.4, 5.3)	1.6 (.6, 4.6)	1.5 (.5, 4.2)	1.0 (.3, 3.4)	1.0 (.2, 6.0)
HPV-68 (n = 20)	0.7 (.1, 3.1)	1.7 (.3, 8.6)	N/E	0.4 (.0, 3.9)	1.4 (.2, 7.9)	N/E
Clade A6						
HPV-56 (n = 122)	1.0 (.5, 1.9)	1.2 (.5, 3.2)	2.0 (.9, 4.2)	1.9 (.9, 3.7)	0.3 (.0, 1.9)	1.3 (.4, 3.9)
HPV-66 (n = 91)	0.9 (.4, 2.1)	1.9 (.6, 6.2)	2.3 (.8, 6.9)	3.4 (1.4, 8.2)	1.0 (.3, 3.9)	1.1 (.2, 5.4)
Clade A5						
HPV-51 (n = 76)	1.5 (.7, 3.0)	2.0 (.7, 5.7)	2.2 (.9, 5.5)	2.2 (1.0, 4.9)	0.8 (.2, 3.0)	1.1 (.3, 4.4)

Abbreviations: HPV, human papillomavirus; HR, high-risk; aMSR, adjusted mean survival ratio; CI, confidence interval; N/A, not an applicable outcome type; N/E, not able to estimate.

[a] Parametric survival regression models adjusted for age (centered at 20 years), bathing frequency, number of sexual partners (in 6 months), consistent condom use (in 6 months), *C. trachomatis* infection.

for all of the HPV types included in the bivalent (HPV-16 and -18) and the quadrivalent (HPV-16, -18, -6, and -11) vaccines than in men with any of these HPV types at baseline.

DISCUSSION

This study presents, to our knowledge, the first epidemiological data in men on the type-specific associations between prevalent HPV infections and future acquisition of other HPV types, to assess the potential for HPV type competition and replacement following widespread prophylactic HPV vaccination. Among 1097 men from Kenya, HPV negativity to the vaccine-relevant HPV types 16, 18, 31, 45, 6, or 11 at baseline was associated with a similar or longer time to acquisition of any other HPV and HR-HPV infections. Type-specific associations between baseline infections and acquisition of individual HR-HPV types varied greatly by HPV type; however, we did not observe a clear pattern of differences in the times to HPV acquisition by the degree of phylogenetic relatedness to the baseline HPV infection. Men without HPV-16, -18, -31, -45, -6, or -11 at baseline did not acquire other HPV infections earlier than men with baseline infections. Therefore, we found no clear evidence to indicate the potential for HPV type competition and replacement.

To better understand which HPV types were contributing to the overall association between prevalent infections and HPV acquisition, we analyzed acquisition of the 14 HR-HPV types separately. There were 47 positive associations (aMSR > 1.1) among the 76 type-specific comparisons, 16 null (aMSR, 0.9–1.1), and 13 negative associations (aMSR < 0.9) between baseline HPV types and type-specific acquisition. Estimates below 1.0 were generally imprecise, with relatively wide CIs that always included 1.0. The wide range in estimates and corresponding 95% CIs for type-specific HPV acquisition indicate that men without baseline infections had a longer time to acquisition for some, but not all, HR-HPV types. For example, men without HPV-16 (clade A9) tended to have shorter time until acquisition of clade A7 types (aMSRs < 1.0) but longer time until acquisition of related types HPV-31 and HPV-58. These findings are consistent with an analysis of the ASCUS/LSIL Triage Study that found among HPV-16–negative women a slight increase in incidence of some clade A7 types and a decrease in incidence of HPV-31 [19].

We observed an overall trend of longer times to acquisition of non–vaccine-preventable HR-HPV among men without any of the vaccine-included HPV types 16, 18, 6, and 11 than in men with any of these 4 HPV types. These findings are consistent with a previous study of women from Colombia,

Table 5. Associations Between Grouped HPV-16, -18, -6, and -11 Infections at Baseline and Acquisition of Individual HR-HPV Types

	Baseline HPV Infection		
HPV Acquisition	HPV-16, -18[a] (n = 136) aMSR (95% CI)[d]	HPV-6, -11[b] (n = 58) aMSR (95% CI)[d]	HPV-16, -18, -6, -11[c] (n = 178) aMSR (95% CI)[d]
Clade A9			
HPV-16		1.7 (.8, 3.5)	
HPV-31	1.8 (.9, 3.7)	2.4 (1.0, 6.1)	1.8 (.9, 3.6)
HPV-33	1.5 (.9, 2.4)	1.1 (.5, 2.4)	1.2 (.7, 2.0)
HPV-35	1.3 (.7, 2.6)	2.4 (1.0, 5.6)	1.4 (.8, 2.6)
HPV-52	1.0 (.5, 2.2)	1.2 (.5, 3.4)	1.1 (.6, 2.1)
HPV-58	3.3 (1.7, 6.3)	1.8 (.7, 4.6)	2.8 (1.5, 5.2)
Clade A7			
HPV-18		1.3 (.6, 2.9)	
HPV-39	0.8 (.4, 1.8)	0.4 (.1, 2.1)	0.7 (.4, 1.5)
HPV-45	0.6 (.3, 1.4)	1.1 (.4, 2.7)	0.8 (.4, 1.4)
HPV-59	0.6 (.3, 1.6)	1.0 (.3, 2.9)	0.8 (.4, 1.7)
HPV-68	1.0 (.3, 3.0)	0.9 (.2, 5.1)	1.0 (.4, 2.8)
Clade A6			
HPV-56	1.1 (.6, 1.9)	0.7 (.3, 1.8)	1.0 (.6, 1.6)
HPV-66	1.1 (.6, 2.4)	1.1 (.4, 3.0)	1.3 (.7, 2.4)
Clade A5			
HPV-51	1.7 (.9, 3.2)	0.9 (.3, 2.5)	1.6 (.9, 2.7)

Abbreviations: HPV, human papillomavirus; HR, high-risk; aMSR, adjusted mean survival ratio; CI, confidence interval; N/A, not an applicable outcome type.

[a] Index group HPV-16 and -18 negative vs referent group HPV-16 and/or -18 positive.

[b] Index group HPV-6 and 11 negative vs referent group HPV-6 and/or -11 positive.

[c] Index group HPV-16, -18, -6, and -11 negative vs referent group HPV-16, -18, -6, and/or -11 positive.

[d] Adjusted for age (centered at 20 years), bathing frequency, number of sexual partners (in 6 months), consistent condom use (in 6 months), *C. trachomatis* infection.

which reported an increased risk of HPV-58 among women with HPV-16 or HPV-18 [11]. It is possible that for comparisons between men who are negative to all 4 HPV types and men with up to 4 HPV type infections, the aMSRs reflect differences in HPV acquisition by risk group or host immunity rather than differences by HPV type. In fact, when we limited our analysis to men with detectable HPV during the study period (n = 965), aMSRs tended to be closer to 1.0, indicating smaller relative differences in time until HPV acquisition between men without each individual HPV type at baseline and those with the specific HPV type (online Supplementary Appendix Table 2).

In epidemiological studies of associations between HPV types, point estimates reflect the combined effect of factors that may increase HPV acquisition, such as unmeasured behavioral risk factors or potential biological facilitation of HPV acquisition by other HPV types [5, 11, 21], and factors that may decrease acquisition among men with prior or prevalent HPV infections, such as host-acquired immunity [20, 21], cross-protection [11, 18, 21], and potential HPV type competition. Because HPV acquisition is strongly related to sexual behavior, we adjusted all estimates for age, recent number of sexual partners, consistent condom use, and laboratory-diagnosed *C. trachomatis* infection, which was previously shown in this population to be associated with multiple HPV infections [40]. In addition, a strength of this prospective study in men is the use of statistical models for interval-censored HPV outcomes that include a random effects frailty term to account for the correlations among acquisition of multiple HPV types that arise from unmeasured sexual behavior and host immunological factors [34]. However, our exposure ascertainment for HPV infection was limited to type-specific HPV status at baseline. Subsequent analyses of HPV type competition might consider modeling infection with vaccine relevant HPV types as a time-varying exposure, although such models are necessarily more challenging to fit and interpret.

Despite the large sample size, a limitation of this study was the small number of infections for rare HPV types, which is reflected in the wide CIs. In addition, the use of GP5+/6+ primers with reverse line blot hybridization may reduce the detection of multiple infections as compared to other detection methods [41, 42], however, it has been shown to reduce cross-hybridization between HPV types [14, 29]. An additional consideration when interpreting the study results is the restriction of our sample to young, uncircumcised men. Our findings may not be generalizable to circumcised males, who may have lower rates of HPV acquisition and multiple infections [27, 43], or to older populations with a longer history of HPV exposure [20]. We examined HPV DNA positivity, not seropositivity, at baseline and acquisition of HPV types not previously detected in the study [44]. It is possible that a previous infection with a specific HPV type could reduce the likelihood of acquiring that type over follow-up [20, 21, 45, 46], which could potentially differ by baseline HPV status. However, men in our study population were young (median age, 20 years) with relatively few lifetime partners (median, 4 partners), and neither of these characteristics differed by baseline status for individual HPV types.

Using data from a large cohort of HIV-uninfected men from Kisumu, Kenya, we contribute to the previous literature in women by presenting data on the associations between baseline HPV infections and acquisition of other HPV types in men. The young male study population is particularly relevant, given that the Food and Drug Administration has recently approved extending HPV vaccine coverage to males aged 9–26 years [10]. Our data indicate that current infections are

generally associated with a slightly shorter time to acquisition of other HPV infections and that men without infections acquire other HPV types later, on average. In terms of individual HPV types, there were no consistently negative associations between specific HPV types that could indicate strong potential for HPV type replacement following HPV vaccination. However, our study of HPV type competition was based on men who were either naturally infected or uninfected (eg unvaccinated men). There may be important immunological differences between individuals who are naturally uninfected, as opposed to protected from infection via vaccination, that could affect acquisition of other HPV types. Ongoing vaccine surveillance studies will provide more definitive data on potential changes in the distribution of non–vaccine-preventable HPV types following widespread HPV vaccination. However, the prevaccine data presented here on the natural patterns of association between HPV types will be extremely useful when interpreting the postvaccine data to attribute any potential changes in nonvaccine types to vaccination as opposed to natural clustering of HPV types.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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