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Type-Specific Human Papillomavirus Prevalence, Incident Cases, Persistence, and Associated Pregnancy Outcomes Among HIV-Infected Women in Kenya

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Background: Persistent infection with high-risk types of human papillomavirus (HPV) is the preeminent factor driving the development of cervical cancer. There are large gaps in knowledge about both the role of pregnancy in the natural history of HPV infection and the impact of HPV on pregnancy outcomes.

Methods: This single-site prospective cohort substudy, nested within an international multisite randomized controlled trial, assessed prevalence, incident cases, and persistence of type-specific HPV infection, and the association between persistence of high-risk HPV infection with pregnancy outcomes among HIV-infected pregnant women in Kenya, including HIV transmission to infants. Type-specific HPV was assessed using a line probe assay in pregnancy and again at 3 months after delivery. HIV status of children was determined using polymerase chain reaction at 6 weeks.

Results: In total, 84.1% (206/245) of women had a high-risk HPV infection at enrollment. Three quarters (157/206) of these infections persisted postpartum. Persistence of HPV16 and/or HPV18 types was observed in more than half (53.4%; 39/73) of women with this infection at enrollment. Almost two-thirds had an incident high-risk HPV infection postpartum, which was not present in pregnancy (62.5%), most commonly HPV52 (19.0%). After adjustments, no association was detected between persistent high-risk HPV and preterm birth. All mothers of the 7 cases of infant HIV infection had persistent high-risk HPV infection ($P = 0.044$).

Conclusions: High levels of high-risk HPV infection and type-specific persistence were documented, heightening the urgency of mass role out of HPV vaccination. The association between HPV persistence and HIV transmission is a novel finding, warranting further study.

Cervical cancer is a largely preventable disease and World Health Organization (WHO) has recently launched a global initiative aimed at eliminating the condition.[1] At present, cervical cancer is the second most common cancer among women aged 15 to 44 years in the world. Persistent infection with high-risk (HR) types of human papillomavirus (HPV) is the preeminent factor driving the development of cervical cancer.[2] More than 75% of sexually active women will experience HPV infection at some time in their life, most of whom will clear the infection within 2 years.[3] Many factors are thought to promote HPV persistence, including smoking, age of sexual debut, number of sexual partners, host immunity, host genetics, HIV infection, infection with other sexually transmitted infections, pregnancy, and use of oral contraceptives.[4–6]

Three highly effective recombinant HPV vaccines have been licensed: a nonavalent vaccine, a quadrivalent vaccine, and a bivalent vaccine. Although coverage with HPV vaccines is growing rapidly in high-income countries, their use in many resource-constrained settings remains limited.[7]

Human papillomavirus genotype distribution differs across geographical areas and populations. Although HPV16 and HPV18 collectively cause 70% of cervical cancer cases in high-income countries, these patterns vary in other settings.[1] A pooled analysis of more than 15,000 women with cervical abnormalities found HPV16 to be more than 2.5 times more common in Europe than in sub-Saharan Africa.[8]

Human papillomavirus prevalence, multiple HPV infections, and HPV viral loads have been found to be substantially higher in

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HIV-infected women when compared with HIV-negative women, including in studies in East Africa.[9–12] In addition, compared with HIV-negative women, precancerous lesions were found to be 3 to 6 times more common in HIV-infected women, including in one study among HIV-infected pregnant women in Africa.[10,13] Human papillomavirus incidence has been reported to be higher among HIV-infected women, who were also less likely to clear the infection.[5,14]

There are many gaps in knowledge about both the role of pregnancy in the natural history of HPV infection and the impact of HPV on pregnancy outcomes. Reported adverse pregnancy outcomes in HPV-infected pregnant women have included preterm deliveries, intrauterine growth retardation, and placental HPV infections.[15–17] Moreover, there is a paucity of studies investigating the role of HPV infection on the vertical transmission of HIV. Mother-to-child transmission of HIV could be more common in HPV-infected women owing to the higher HIV viral load levels observed among pregnant women with HPV and cervical lesions caused by HPV.[18] It is also plausible that HIV takes advantage of the placental damage caused by HPV to infect the infant, but this remains unproven.

Considering the overlap in the HPV and HIV epidemics, an HPV investigation was nested within the Kesho Bora trial, which was designed primarily to assess the efficacy and safety of a triple-antiretroviral-drug regimen administered during pregnancy and continued throughout breastfeeding on Mother-To-Child-Transmission of HIV (MTCT).[19,20] This article presents findings from this substudy, specifically, a longitudinal assessment of HPV type–specific prevalence, incident infections, persistence and clearance, and the relationship between HR-HPV infection and birth outcomes among HIV-infected pregnant women in Kenya.

MATERIALS AND METHODS

Study Population and Intervention

This analysis was nested within the Kesho Bora study for which the design, population, and results are described elsewhere.[19–21] Data are reported here from 245 HIV-1–infected pregnant women in Mombasa, Kenya, 1 of the 5 sites of the Kesho Bora trial. This analysis includes participants enrolled in the observational cohorts of the study and the randomized controlled trial components of the study, where women were assigned to a triple antiretroviral regimen or a short-course dual-drug regimen for prophylaxis against MTCT.[20,21]

In brief, women were recruited from antenatal clinics and eligible for the study if they were at 36 weeks' gestation or less, were confirmed HIV infected, were residing and planning to continue to reside in the study site catchment area until 2 years after delivery, and had no evidence of clinically significant conditions. At the enrollment visit, eligible women were asked to sign an informed consent form, including that for long-term storage of cervical aspirate samples.

Study Procedures

Women were followed up throughout pregnancy and up to 24 months after delivery. During the antenatal period, women were asked to attend the clinic every 2 weeks from enrollment until delivery, as well as mother-infant pairs at the same frequency during the first 8 weeks of the postpartum period, then monthly until 1 year and every 3 months thereafter.

Using face-to-face structured interviews, information including sociodemographics, sexual behavior, and reproductive history was collected at enrollment, and blood samples were taken for immunological (CD4 cell count) assessments. Children's HIV-1 infection status was determined at the age of 6 weeks using a quantitative HIV-1 RNA real-time polymerase chain reaction assay (Generic HIV-1 Charge Virale, Biocentric, Bandol, France).

All women were screened using a Papanicolaou (Pap) test at 3 months postpartum. Cytological classification was done according the Bethesda classification, and women were given follow-up care as per WHO recommendations.[22]

Maternal HPV infection and typing was determined at 2 time points, firstly at enrollment and subsequently at 3 months after delivery. Women enrolled in the study were tested for 28 different HPV genotypes, composed of 14 HR-HPV and 14 low-risk (LR) HPV. Cervical samples were obtained by using a syringe to introduce 10 mL of normal saline directed at the os to bath the cervix and ectocervix. The fluid was allowed to pool into the posterior fornix and aspirated into the same syringe.[23] This was repeated 5 times with the same fluid, which was then transferred to a sterile 15-mL conical test tube. The samples were transported to the laboratory within an hour of collection. Upon arrival at the laboratory, the samples were centrifuged at 3000 rpm for 10 minutes at 4°C. The acellular fraction was recovered, aliquoted, and stored at −80°C. The pellet was resuspended in 1 mL of sterile phosphate-buffered saline and centrifuged at 3000 rpm for 10 minutes at 4°C. The supernatant was discarded, whereas the dry pellet was stored at −80°C. Human papillomavirus DNA was extracted from the resuspended pellet in molecular biology grade water using the Qiagen DNA mini kit. Human papillomavirus detection and typing was performed using the INNO-LiPA HPV Genotyping Extra assay (Innogenetics, Ghent, Belgium) according to the manufacturer's instructions. The LiPA assay covers 28 HPV genotypes, including HR-HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 69, and LR-HPV types 6, 11, 26, 40, 43, 44, 53, 54, 66, 70, 71, 73, 74, and 82. The hybridization patterns on the strips were interpreted by 2 independent readers.

Study Measures

Human papillomavirus–related study end points included HPV prevalence, incident infections, persistence, and clearance. We present each of these end points by HPV type, LR-HPV and HR-HPV categories, and overall measures. Incident HPV infection was defined as a newly detected HPV genotype at the postdelivery assessment among women previously negative for that genotype. Human papillomavirus persistence was defined as a positive test result for the same genotype at both the antenatal and the postdelivery assessments, and could be due to reinfection with the same type. Human papillomavirus clearance was defined as a positive test result during the antenatal period followed by a negative test result for the same genotype at the postdelivery assessment.

Associations between HR-HPV infection and adverse infant outcomes were assessed, including preterm birth (birth before 37 weeks' gestation), low birth weight (any live born infant weighing <2.5 kg, regardless of gestational age), and infant HIV infection at 6 weeks of age.

The duration since women discovered their HIV infection status was dichotomized as less or more than 6 months before study enrollment. Socioeconomic status quintiles were constructed based on 9 measures, including household goods, amenities, and source of water and electricity.

Data Analysis

Data were double entered and analyzed using Stata SE 13 (Stata Corporation, College Station, TX). Descriptive analysis of

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the population characteristics assessed the distribution of continuous variables and the frequency distribution of categorical variables in contingency tables. χ^2 Tests were used for analysis of categorical variables, whereas for continuous variables, we used Student *t* test or Wilcoxon rank sum tests, as applicable.

Using multivariable logistic regression models, we investigated whether certain prespecified sociodemographic, clinical, and obstetric variables of interest were independent predictors of HR-HPV persistence. We only assessed factors associated with persistence, as this is the most important risk factor for cervical cancer. In a separate multivariable logistic regression analysis, we assessed whether HR-HPV persistence was associated with preterm delivery, low birth weight, and mother-to-child transmission of HIV.

Ethics

Ethical approval for study procedures was given by the Kenyatta National Hospital ethical review board in Kenya, as well as the ethical review committee at the WHO.

RESULTS

Participant Characteristics

A total of 245 HIV-1–infected pregnant women were enrolled in Mombasa, Kenya, and had HPV typing information available. At enrollment, these women were aged 17 to 42 years, and most (91.8%) were married or had a regular partner (Table 1). Gestational age at enrollment was a median 33 weeks (interquartile range, 32–33 weeks), with 93% of women in their third trimester. Most women (83.3%; 204/245) had received their HIV diagnosis within the last 6 months, and 60.4% (148) were classified as clinical HIV stage 1. Information on sexual behavior was available for 78% (191/245) of women enrolled in the study. Approximately half of women (53.9%) were sexually active at 3 months after delivery, and 40.8% (42/103) of these reported unprotected sex with any partner since childbirth.

HPV Prevalence

Nearly all women (98.4%; 241/245) enrolled in this study had infection with 1 or more HR-HPV and/or LR-HPV type. Among those infected with any HPV type, 85.5% (206/241) carried at least 1 HR-HPV type. In total, 78.5% had more than 1 HPV type.

During pregnancy, the most prevalent HR-HPV types were HPV52 (43.8%), HPV51 (26.1%), HPV16 (18.0%), HPV35 (13.5%), and HPV18 (13.5%; Fig. 1 and Table 2). At enrollment, LR-HPV types 6 and 11 were detected in 8.6% and 4.5% of women, respectively. Of all participants, almost one-third (29.8%) were carrying HPV16 and/or HPV18 at baseline. Multiple infections involving HPV6, HPV11, HPV16, and HPV18 (covered by the HPV vaccine Gardasil) were detected in 38.4% of the study participants.

High-risk HPV types 52, 51, 16, 35, and 18 were still the most prevalent at 3 months postpartum (Fig. 1). Prevalence of any HPV infection decreased by 32% over the follow-up period.

None of the baseline sociodemographic characteristics of the study participants were associated with an increased risk of HR-HPV infection at baseline, with the exception of marital status ($P = 0.009$; Table 1).

HPV Persistence, Clearance, and Incident Infection

The presence of HPV between the antenatal period and 3 months postpartum was assessed for HR-HPV and LR-HPV types (Table 2). Among participants who had any HR-HPV detected during pregnancy, HR-HPV persistence of 1 or more types was observed in 76.2% (157/206). Depending on the type, HPV persistence of the individual HR types varied between 41.7% and 72.7%. Persistence of 16 and/or 18 types was observed in more than half (53.4%; 39/73) of women with this infection at enrollment. Most demographic or clinical factors were not associated with HR-HPV persistence (Table 3). When adjusted for potential confounders, age was found to be associated with HR-HPV persistence, with women aged 30 to 34 years more likely to have persistent HR-HPV infection than their younger counterparts aged 16 to 24 years ($P = 0.013$).

Overall, types 11, 68, 51, and 45 were the most likely to be cleared by infected women, in the proportions of 81.8%, 58.3%, 54.7%, and 50.0%, respectively (Table 2). Of 94 women with 1 or more of infections involving HPV6, HPV11, HPV16, and HPV18, almost half of the cases (47.9%) cleared 1 or more of these infections.

The proportion with an HPV incident infection of any HR type was 62.5%. In decreasing order, the top 5 HR-HPV incident infections were HPV52 (19.0%, 19 new infections), HPV51 (11.1%, 20 new infections), HPV16 (9.5%, 19 new infections), HPV35 (7.1%, 15 new infections), and HPV68 (6.1%, 14 new infections). There were 27 new cases of HPV16 and/or HPV18 (19 acquired HPV18, 9 HPV16, and 1 both HPV16 and HPV18).

Pap Test Results

In total there were 222 valid Pap test results at 3 months after delivery (7 were not done and 16 results were indeterminate). Of all women, 27.5% (61/222) had an abnormal result: 24 had atypical squamous cells of undetermined significance (10.8%), 27 had low-grade squamous intraepithelial lesions (12.2%), 10 had high-grade squamous intraepithelial lesions (4.5%), and none had evidence of invasive cervical carcinoma. Of 144 women with persistent HR-HPV infection, 31.3% (45) had an abnormal Pap test result at 3 months after delivery compared with 20.5% (16/78) of women with no or nonpersistent HR-HPV. When adjusted for potential confounders, this difference was not statistically significant, with women with persistent HR-HPV being 1.77-fold more likely to have an abnormal Pap test result (adjusted odds ratio [AOR]; 95% confidence interval [CI], 0.87–3.60; $P = 0.115$).

Perinatal and Postnatal Outcomes

Overall, 15.5% (38/245) of childbirths were preterm. There was no association between persistent HR-HPV and preterm birth when adjusted for age, education, socioeconomic status, number of children, duration since HIV diagnosis, CD4 count, WHO clinical staging, and antiretroviral regimen used (AOR, 1.0; 95% CI, 0.5–2.2; $P = 0.99$). One in 10 of the infants for whom a birth weight was recorded (22/222) were categorized as low birth weight. Babies born to women with persistent HR-HPV were more likely to weigh less than 2.5 kg at birth (12.8% vs. 4.9%). However, after controlling for potential confounders, this difference was no longer statistically significant (AOR, 4.2; 95% CI, 0.84–21.1; $P = 0.081$).

A total of 9 women transmitted HIV infection to their children by 6 weeks postpartum. Human papillomavirus data were not available for 2 of these women. In analysis with the

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TABLE 1. Characteristics of HIV-Infected Women and HPV Characteristics at Enrollment (During Pregnancy) in the Kesho Bora Study in Mombasa, Kenya (N = 245)

Variable	All Women (N = 245), n/N (%)*	HPV Infection, n/N (%)*		
		Any High-Risk HPV Infection (n = 206)	No High-Risk HPV Infection (n = 39)	$P^{\dagger}$
Age, mean (SD), y	28.0 (4.9)	28.1 (4.8)	27.2 (5.3)	0.28‡
Education level				
Never attended school	12/245 (4.9)	10/206 (4.9)	2/39 (5.1)	
Primary	133/245 (54.3)	111/206 (53.9)	22/39 (56.4)	
Secondary or higher education	100/245 (40.8)	85/206 (41.3)	15/39 (38.5)	0.95
Current marital status				
Married, regular partner	225/245 (91.8)	193/206 (93.7)	32/39 (82.0)	
Separated, divorced, widowed	7/245 (2.9)	6/206 (2.9)	1/39 (2.6)	
Single	13/245 (5.3)	7/206 (3.4)	6/39 (15.4)	0.009
Current work status				
Working	82/245 (33.5)	73/206 (35.4)	9/39 (23.1)	
Not working	163/245 (66.5)	133/206 (64.6)	30/39 (76.9)	0.13
Regular partner's current work status				
Formal sector	109/225 (48.4)	94/193 (48.7)	15/32 (46.9)	
Informal sector	105/225 (46.7)	89/193 (46.1)	16/32 (50.0)	
Regular partner not working	11/225 (4.9)	10/193 (5.2)	1/32 (3.1)	0.84
Socioeconomic status, wealth quintiles				
Q1	46/245 (18.8)	37/206 (17.9)	9/39 (23.1)	
Q2	52/245 (21.2)	44/206 (21.3)	8/39 (20.5)	
Q3	48/245 (19.6)	41/206 (19.9)	7/39 (18.0)	
Q4	47/245 (19.2)	36/206 (17.4)	11/39 (28.2)	
Q5 (wealthier quintile)	52/245 (21.2)	48/206 (23.3)	4/39 (10.3)	0.27
Duration in relationship, y				
<2 y	36/223 (16.1)	34/191 (17.8)	2/32 (6.3)	
2–4	77/223 (34.5)	67/191 (35.1)	10/32 (31.3)	
≥5	110/223 (49.3)	90/191 (47.1)	20/32 (62.5)	0.16
No. live children				
None	82/245 (33.5)	65/206 (31.6)	17/39 (43.6)	
1	73/245 (29.8)	64/206 (31.1)	9/39 (23.1)	
2	48/245 (19.6)	42/206 (20.4)	6/39 (15.4)	
≥3	42/245 (17.1)	35/206 (17.0)	7/39 (18.0)	0.47
Duration since first tested HIV positive, mo				
<6	204/245 (83.3)	174/206 (84.5)	30/39 (77.0)	
≥6	41/245 (16.7)	32/206 (15.5)	9/39 (23.1)	0.25
HIV status of regular partner				
Never tested	125/226 (55.3)	109/194 (56.2)	16/32 (50.0)	
Don't know if ever tested	27/226 (12.0)	25/194 (12.9)	2/32 (6.3)	
Ever tested	74/226 (32.7)	60/194 (30.9)	14/32 (43.8)	0.28
HIV negative	32/74 (43.2)	23/60 (38.3)	9/14 (64.3)	
HIV positive	37/74 (50.0)	32/60 (53.3)	5/14 (35.7)	
Unknown status partner	5/74 (6.8)	5/60 (8.3)	0/14	0.16
CD4 cells, median count (IQR)	350 (275–429)	351 (276–428)	341 (222–451)	0.85§
WHO clinical HIV stage				
Stage 1	148/245 (60.4)	121/206 (58.7)	27/39 (69.2)	
Stage 2	79/245 (32.2)	72/206 (35.0)	7/39 (18.0)	
Stage 3	14/245 (5.7)	9/206 (4.4)	5/39 (12.8)	
Stage 4	4/245 (1.6)	4/206 (1.9)	0/39	0.039
Antiretroviral drugs				
Antiretroviral therapy	32/245 (13.1)	26/206 (12.6)	6/39 (15.4)	
Triple ARV MTCT prophylaxis	115/245 (46.9)	92/206 (44.7)	23/39 (59.0)	
Short-course MTCT prophylaxis	98/245 (40.0)	88/206 (42.7)	10/39 (25.6)	0.13

*n/N (%) was presented unless otherwise indicated.

†χ^2 Tests unless otherwise indicated.

‡Student *t* test.

§Wilcoxon rank sum tests.

ARV MTCT indicates antiretroviral mother-to-child transmission; IQR, interquartile range; WHO, World Health Organization.

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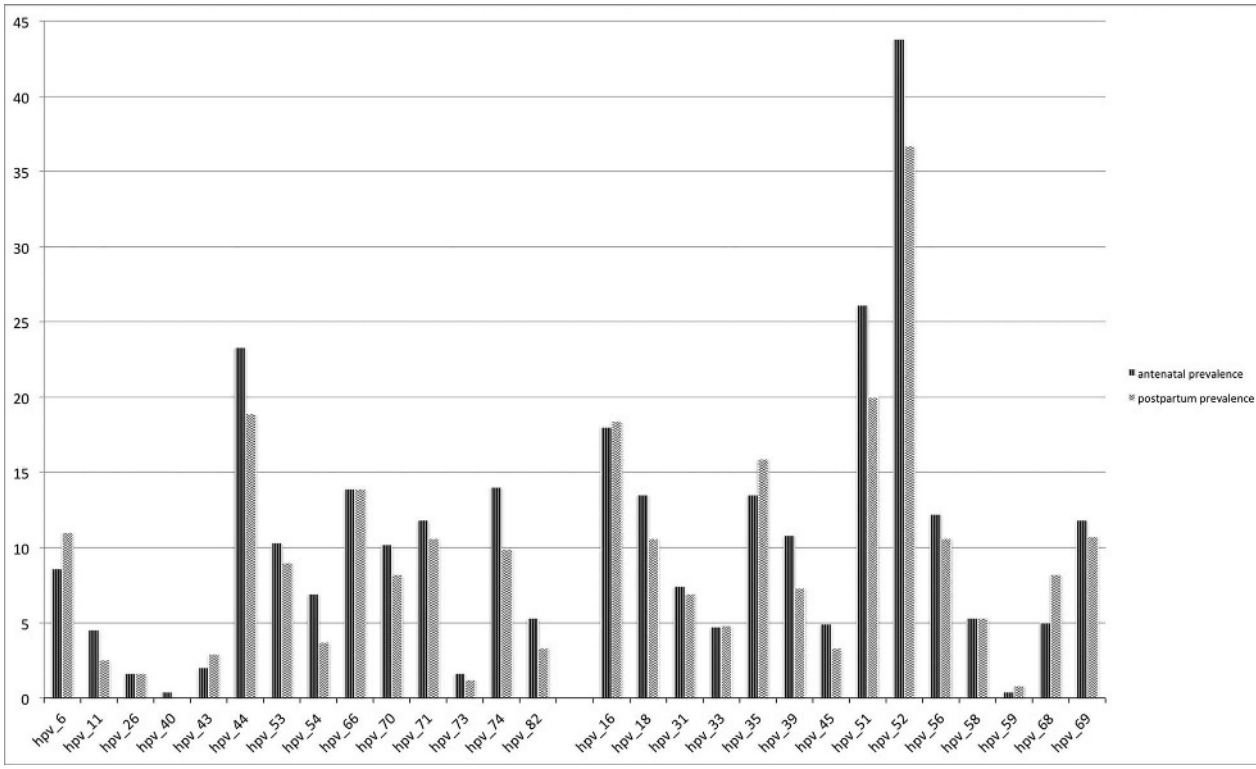


Figure 1. Prevalence of type-specific low-risk and high-risk HPV infections during pregnancy and at 3 months after delivery among HIV-infected women in Kenya.

remaining cases, women with persistent HR-HPV were more likely to transmit HIV to their child than all other women ($P = 0.044$), a finding that persisted in multivariate analysis. In all these 7 cases of mother-to-child transmission, the mothers had persistent HR-HPV infection (7/157 [4.5%] vs. 0/of 88 women without persistence). An abnormal Pap test result was also associated with transmission of HIV infection from mother to child ($P = 0.026$).

TABLE 2. Type-Specific HPV Prevalence in HIV-Infected Kenyan Women at Enrollment (During Pregnancy), and Persistence, Clearance, and Incident Infections at 3 Months After Delivery

HPV Type	Prevalence at Enrollment, n/N (%)	Persistence, n/N (%)	Clearance, n/N (%)	Incident Infections, n/N† (%)
Individual low-risk HPV type				
6	21/245 (8.6)	11/21 (52.4)	10/21 (47.6)	16/224 (7.1)
11	11/245 (4.5)	2/11 (18.2)	9/11 (81.8)	4/234 (1.7)
Individual high-risk HPV type				
16	44/245 (18.0)	26/44 (59.1)	18/44 (40.9)	19/201 (9.5)
18	33/245 (13.5)	17/33 (51.5)	16/33 (48.5)	9/212 (4.3)
31	18/245 (7.4)	12/18 (66.7)	6/18 (33.3)	5/227 (2.2)
33	11/235 (4.7)	6/11 (54.6)	5/11 (45.5)	4/214 (1.9)
35	33/245 (13.5)	24/33 (72.7)	9/33 (27.3)	15/212 (7.1)
39	22/203 (10.8)	12/22 (54.6)	10/22 (45.5)	5/168 (3.0)
45	12/245 (4.9)	6/12 (50.0)	6/12 (50.0)	2/233 (0.9)
51	64/245 (26.1)	29/64 (45.3)	35/64 (54.7)	20/181 (11.1)
52	84/192 (43.8)	55/84 (65.5)	29/84 (34.5)	19/100 (19.0)
56	30/245 (12.2)	16/30 (53.3)	14/30 (46.7)	10/215 (4.7)
58	13/245 (5.3)	8/13 (61.5)	5/13 (38.5)	5/232 (2.2)
59	1/245 (0.4)	1/1 (100)	0/1 (0)	1/244 (0.4)
68	12/241 (5.0)	5/12 (41.7)	7/12 (58.3)	14/228 (6.1)
69	29/245 (11.8)	17/29 (58.6)	12/29 (41.4)	9/215 (4.2)
One or multiple HPV types*				
16/18	73/245 (29.8)	39/73 (53.4)	34/73 (46.6)	27/241 (11.2)
6/11/16/18	94/245 (38.4)	49/94 (52.1)	45/94 (47.9)	45/245 (18.4)
Any high-risk HPV	206/245 (84.1)	157/206 (76.2)	49/206 (23.8)	153/245 (62.5)

*Proportion of participants with infection with one or more HPV types. Changes in denominators by HPV type are due to cases of invalid type-specific results. †Infection with an HPV type at postdelivery that was not present at enrollment, includes only cases with results at both visit.

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DISCUSSION

This was the first large-scale longitudinal study investigating the relationship between HPV and pregnancy outcomes in HIV-infected women in Africa, to our knowledge. The prevalence of HR-HPV found in this study at enrollment (84.1%) was 2.5 times higher than that reported in a meta-analysis among the general population in East Africa and considerably higher than the prevalence reported in a systematic review of HPV studies in Kenya.[24,25]

The type-specific prevalence in this study is consistent with other genotype surveys conducted among HIV-infected women in East Africa, with the most commonly detected HR genotype being HPV52.[10,12,14] However, the overall distribution of HPV infections differs from some studies that show HR-HPV types 56 and 58 to be among the most common genotypes in HIV-infected Kenyan women.[10,12] This may, in part, be due to differing HPV detection methods between studies. Although HPV types 16 and 18 are the most prevalent in the general population as well as being associated with most cervical cancer cases worldwide,[24,26] our study is consistent with the evidence that indicates a different type-specific prevalence of HPV in HIV-infected individuals.[10,12,27] The prevalence of HPV16 and/or HPV18 in our study participants was almost 30%, which is considerably higher than that in a similar population in Nairobi, where approximately 8% of women had HPV16 and/or HPV18.[12] A total of 38.4% of women in this study were infected with 1 or more of the 4 types in the quadrivalent HPV vaccine (HPV16, HPV18, HPV6, and HPV11), and a considerable additional number of women would be covered by the nonovalent vaccine, which includes HPV52, for example, the most prevalent HR-HPV type in this population. However, more than one quarter and more than 1 in 10 women were infected with HPV51 and HPV35, respectively, neither of which are included in current HPV vaccines, although some cross-protection is possible across HPV types.[28] Given this prevalence in an HR population, it may be worth considering the inclusion of these types if future HPV vaccines include additional HPV types.

Persistent HR-HPV infection is the preeminent risk factor for cervical cancer.[2] Our finding that more than three quarters of HR-HPV infections in this population of HIV-infected pregnant women persisted until at least 3 months postpartum is therefore concerning. It is, however, difficult to directly compare these findings with other studies because definitions of HPV persistence and duration of follow-up vary between studies.[29]

Consistent with the existing literature, the proportion of LR-HPV cases that were cleared was higher than that with HR-HPV types (81.4% cleared compared with 58.3%).[14] We report type-specific clearance and persistence, such that one woman who is infected with multiple types at baseline could still be

TABLE 3. Univariable and Multivariable Analyses of Factors Associated With Persistence (or Reinfection) of 1 or More HR-HPV Types Between Antenatal Period and Postpartum Period Among HIV-Infected Pregnant Women With HR-HPV Infection at Enrollment in Kenya (n = 206)

	n/N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)*	*P*
Age, y				
16–24	38/56 (67.9)	1.0	1.0	
25–29	53/69 (76.8)	1.6 (0.7–3.5)	1.9 (0.7–4.9)	0.21
30–34	52/62 (83.9)	2.5 (1.0–6.1)	4.0 (1.3–12.5)	0.018
≥35	14/19 (73.7)	1.3 (0.4–4.3)	2.3 (0.5–10.3)	0.27
Education level				
Never attended school	8/10 (80.0)	1.0	1.0	
Primary	84/111 (75.7)	0.8 (0.2–3.9)	0.7 (0.1–3.7)	0.66
Secondary or higher education	65/85 (76.5)	0.8 (0.2–4.2)	0.6 (0.1–3.7)	0.58
Current marital status				
Married, regular partner	146/193 (75.7)	1.0	1.0	
Separated, divorced, widowed	5/6 (83.3)	1.6 (0.2–14.2)	0.7 (0.06–7.4)	0.75
Single	6/7 (85.7)	1.9 (0.2–16.6)	2.3 (0.2–24.1)	0.49
Socioeconomic status				
1	30/37 (81.1)	1.0	1.0	
2	33/44 (75.0)	0.7 (0.2–2.1)	0.8 (0.2–2.5)	0.64
3	33/41 (80.5)	1.0 (0.3–3.0)	1.1 (0.3–3.8)	0.86
4	23/36 (63.9)	0.4 (0.1–1.2)	0.3 (0.1–1.0)	0.054
5 (wealthier quintile)	38/48 (79.2)	0.9 (0.3–2.6)	0.8 (0.2–2.6)	0.71
No. live children				
None	47/65 (72.3)	1.0	1.0	
1	52/64 (81.3)	1.7 (0.7–3.8)	1.8 (0.7–4.5)	0.20
≥2	58/77 (75.3)	1.2 (0.6–2.5)	0.7 (0.3–2.0)	0.57
Duration since first tested HIV positive, mo				
0–5	134/174 (77.0)	1.0	1.0	0.52
≥6	23/32 (71.9)	0.7 (0.3–1.8)	0.7 (0.3–1.9)	
WHO clinical HIV staging				
Stage 1	90/121 (74.4)	1.0	1.0	
Stage 2	56/72 (77.8)	1.2 (0.6–2.4)	1.2 (0.6–2.7)	0.57
Stage 3 or 4	11/13 (84.6)	1.9 (0.4–9.1)	1.8 (0.3–10.6)	0.54
Antiretroviral drugs				
Antiretroviral therapy	23/26 (88.5)	3.2 (0.9–11.8)	2.5 (0.6–10.6)	0.21
Triple ARV MTCT prophylaxis	69/88 (78.4)	1.5 (0.8–3.0)	1.6 (0.7–3.4)	0.24
Short MTCT prophylaxis	65/92 (70.7)	1.0	1.0	

*Associations were adjusted for all potential confounding factors included in the final multivariable model.

ARV MTCT indicates antiretroviral mother-to-child transmission; OR, odds ratio.

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classified as having cleared a type-specific infection, even when another type was found to persist. It has been well established in the literature that HPV clearance is less frequent among HIV-infected women compared with the general population, and that they take significantly longer periods of time to clear infections.[5,30] Almost one quarter (23.8%) of the women in this study had cleared a type-specific HR-HPV infection at 3 months postpartum. Other studies have shown that high viral load, low CD4 count, smoking and oral contraceptive use are all independent risk factors for low rates of and prolonged time to HPV clearance.[4,30] Our study did not find an association between CD4 count and HPV persistence, potentially because of the low number of women with a CD4 count less than 200 cells/mm^3. Smoking status and oral contraceptive use were not measured in this study; however, the prevalence of oral contraceptives is likely to be low in pregnant and postpartum women, and smoking is rare among Kenyan women (estimated to be <1%).[31] Our findings did show an association between age and HPV persistence, with women aged 30 to 34 years more likely to have HR-HPV persistence than women aged 16 to 24 years. The reason for this is unclear, although potentially these older women may have been infected with HIV for longer than the younger group, even if they were unaware of their diagnosis.

This study found that incident infections with any type of HPV occurred in 41.2% of women, with the most common 3 types being consistent with those detected at baseline. This is a similar finding to a study in Kampala, Uganda, which found that 48% of HIV-infected pregnant women had had an incident HPV infection over the course of pregnancy.[14] In our study, incident infections with HPV52, HPV51, and HPV16 were evident in 19%, 11.1%, and 9.5% of women, respectively. Safaeian et al.[5] found similar results in Uganda, with HPV51 and HPV16 having the highest incidence rates in HIV-infected women. Potentially, if all the participants in our study had received the quadrivalent HPV vaccine Gardasil, 18.4% of incident infections might have been prevented.

In our study, we did not detect an association between HR-HPV persistence and preterm delivery, unlike in several other studies.[15,16] Differences between these findings and our study may be related to varying definitions of preterm delivery, difficulties in accurately estimating gestation in many settings, and already high risks of preterm delivery in HIV-infected women.[32] High-risk HPV infection has also been associated with premature rupture of membranes in some studies[33] but was not assessed in our study. We did find an increased risk of low birth weight in infants born to women with persistent HR-HPV infection in bivariate analysis and a trend in multivariate analysis. These concerns have been raised in previous studies[17] and require further investigation, especially in settings where low birth weight is a major risk factor for infant mortality.

This study is the first, to our knowledge, to show an association between persistent HR-HPV infection in HIV-infected pregnant women and the transmission of HIV from mother to child. This finding is consistent with evidence that maternal infection with other sexually transmitted diseases, such as syphilis and herpes simplex virus type 2, increases the risk of mother-to-child transmission of HIV.[34,35] In one study, as much as 28% of mother-to-child transmission of HIV was attributed to herpes simplex virus type 2 infection.[34] The mechanism for this is thought to be related to ulcers and lesions in the genital tract caused by these infections. Persistent HR-HPV has also been linked with the presence of cervical abnormalities, with an even stronger association in HIV-infected women.[2,26] There are also considerable synergistic relationships between HPV and HIV, reinforcing the impact of each other.[36] It is important to note that associations between HPV persistence and MTCT in women receiving antiretroviral drugs during pregnancy, as in this study, are likely to differ from associations in pregnant women not receiving these drugs.[37]

There are a number of limitations that must be considered. Women classified as having HR-HPV persistence at follow-up could in fact have cleared the infection and then have been reinfected with the same HR-HPV type. Most previous studies suggest that women are more likely to clear HPV infections after childbirth rather than during pregnancy, with most infections being cleared within 2 years postpartum.[30] Our results would differ from those of an assessment at 12 or 18 months postpartum had we done so.

In conclusion, our study shows a worryingly high prevalence of persistent HR-HPV in HIV-infected women in Mombasa. The consequent increased risk of cervical cancer in these women is concerning and warrants further research, heightened access to HPV vaccination, and considerably increased efforts to prioritize this public health issue. The nonovalent vaccine holds particular promise in this setting, although further HPV types may need to be included to obtain maximum protection. The finding that HR-HPV persistence is associated with mother-to-child transmission of HIV is notable and should be investigated further.

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