

Infection with Human Papillomavirus and HIV among Young Women in Kampala, Uganda

Cecily Banura,^{1,4} Silvia Franceschi,⁵ Leen-Jan van Doorn,⁶ Annie Arslan,⁵ Fred Wabwire-Mangen,² Edward K. Mbidde,³ Wim Quint,⁶ and Elisabete Weiderpass,^{4,7,8}

¹Faculty of Medicine, Makerere University, ²School of Public Health, Makerere University, Kampala, ³Virus Research Institute, Entebbe, Uganda; ⁴Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; ⁵International Agency for Research on Cancer, Lyon, France; ⁶DDL Diagnostic Laboratory, Voorburg, The Netherlands; ⁷Cancer Registry of Norway, Oslo, Norway; ⁸Samfundet Folkhalsan, Helsinki, Finland

Background. Information on the prevalence of cervical infection with different human papillomavirus (HPV) types among young women is essential to support the introduction of HPV vaccine in Uganda.

Methods. Cross-sectional findings are presented from a cohort study of 1,275 sexually active women aged 12–24 years seeking health services at a clinic for teenagers in Kampala, Uganda. We assessed the presence of 39 HPV types by use of highly sensitive polymerase chain reaction assays.

Results. The prevalence of HPV infection was 74.6%, and the prevalence of human immunodeficiency virus infection was 8.6%. High-risk HPV types were found in 51.4% of women, and the most frequently detected high-risk types were, in decreasing order, HPV 52, 51, 18, and 16. A total of 71.8% of the women who were positive for HPV 16 and/or 18 were also infected with other high-risk HPV types. HIV-positive women had a higher prevalence of HPV infection (87.8% vs 73.2%) and of multiple-type infections (64.6% vs 37.3%), compared with HIV-negative women. Employment in the tertiary sector, lifetime number of sexual partners, concurrent pregnancy, and the presence of genital warts were significantly associated with HPV positivity.

Conclusions. The prevalence of HPV infection is high among young women in Kampala, Uganda. Clinics for teenagers provide an opportunity to monitor the impact of HPV vaccines and, possibly, to catch up unvaccinated young women who have recently become sexually active.

Cervical cancer is very frequent in sub-Saharan Africa, and in Kampala, Uganda, the age-standardized rate of cervical cancer is 40.7 cases per 100,000, one of the highest rates in the world [1]. Immune suppression caused by HIV infection, which is also common in sub-Saharan Africa, is associated with an especially high prevalence of human papillomavirus (HPV) infection [2], and women infected with HIV are at significantly increased risk for precancerous and cancerous lesions of the cervix [3, 4].

Vaccines to prevent HPV infection hold the promise of a significant reduction in HPV infection and its cancer sequelae, and an HPV vaccine demonstration project is planned for Uganda [5]. However, essential information on the infection burden, age at first infection, and distribution of different HPV types in Uganda is lacking. The only previous information on the prevalence of HPV infection in Uganda derives from a community-based study of 960 women aged 15–59 years that was carried out during 1996–1997 in the Rakai District, a rural area [6]. Therefore, we started a cohort study on the prevalence of HPV infection among sexually active young women in Kampala, Uganda. In this article, we report our findings at study enrolment.

SUBJECTS AND METHODS

Study population and setting. Young women presenting themselves for health services at the Naguru Teenage Information and Health Centre, located in a suburb of Kampala, Uganda, between September 2002 and November 2004, were invited to join the study. All

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Reprints or correspondence: Dr. Cecily Banura (c/o Dr. Weiderpass), Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, PO Box 281, 171 77 Stockholm, Sweden (c/o Dr. Weiderpass eliwei@ki.se).

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sexually active women aged less than 25 years who had resided within a 20-kilometer radius of the clinic for the previous 6 months were considered eligible for the study.

Trained midwives explained the study's aims and procedures, which included answering a questionnaire and having a pelvic examination. After obtaining informed consent, the young women were interviewed in English or Luganda (the most common local dialect). The questionnaires included detailed questions on socio-demographic characteristics, use of cigarettes and illicit drugs, reproductive and menstrual factors, sexual behavior and history of sexually transmitted diseases among women and their partner(s), and use of contraceptive methods. Before pelvic examination all women were offered pretest counselling for HIV, and testing for HIV, syphilis and pregnancy.

Gynecological examination and collection of exfoliated cervical cells and blood. Trained midwives performed a pelvic examination and recorded abnormalities according to a standardized protocol [7]. After visual inspection of the vulva, a non-lubricated sterile speculum was inserted, and exfoliated cervical cells were collected with a sterile swab (Copan International), which was then placed in labeled 15-mL holding tubes containing 5 mL of PBS (pH, 7.2). Samples were kept temporarily at 4°C for an average of 6 hours and then transferred to a freezer and kept at -20°C until shipment. Before removal of the speculum, visual inspection of the cervix with acetic acid (VIA) and with Lugol iodine (VILI) was performed [8]. A urine sample and 4 mL of blood (in heparinized tubes) were collected.

Women who had external genital warts were treated with 2% podophyllin paint. Women with vaginal discharge and cervicitis received a 1-week syndromic treatment that included antibiotics, metronidazol, and topical antifungal medication. Women were also asked to talk to their sexual partners and to come back after treatment. Of 3 women who were suspected to have cervical cancer at the time of VIA and VILI inspection and after biopsy, 2 were found to be histologically normal, although a histologically-confirmed stage IIIB cervical cancer was detected in a 23-year-old woman who subsequently underwent palliative radiotherapy.

Isolation of HPV DNA. Exfoliated cell samples were shipped in dry ice to DDL Diagnostic Laboratory (Voorberg, The Netherlands). Total DNA was isolated from 200 μ L of the suspension containing the cervical cells by use of the MagNA Pure LC instrument (Roche Diagnostics), using the Total DNA isolation kit (Roche Diagnostics). DNA was eluted in 100 μ L of water, and 10 μ L was used for each polymerase chain reaction (PCR). Each run contained positive and negative controls to monitor the DNA isolation, PCR, HPV detection, and genotyping procedures.

PCR testing. The short PCR fragment (SPF)₁₀ primer set was used to amplify a broad spectrum of HPV genotypes, as described earlier [9, 10]. Briefly, this primer set amplifies a fragment of 65 bp from the L1 region of HPV. Reverse primers con-

tain a biotin label at the 5' end, enabling capture of the reverse strand onto streptavidin-coated microtiter plates. Captured amplicons were denatured by alkaline treatment, and the captured strand was detected by a defined cocktail of digoxigenin-labelled probes, which detects a broad spectrum of HPV genotypes. This method is called HPV DNA enzyme immunoassay (DEIA), and it provides an optical density value. If the SPF₁₀-DEIA yielded a borderline value (75%–100% of the cut-off value), the SPF₁₀ PCR was repeated and retested by DEIA.

The same SPF₁₀ amplicons can be used to identify the HPV genotype by reverse hybridization on a reverse-hybridization line probe assay (LiPA) that contains probes for 25 different HPV genotypes (SPF₁₀ HPV LiPA, version 1; Labo Bio-medical Products; capable of detecting HPV 6, 11, 16, 18, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68/73, 70, and 74). Samples that were positive at SPF₁₀ PCR primer but did not reveal any of the 25 aforementioned types were provisionally classified as positive for HPV X and subjected to a second reverse-hybridization assay for 17 additional types (26, 30, 55, 61, 62, 64, 67, 69, 71, 82, 83, 84, 85, 87, 89, 90, and 91). HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 were considered high-risk types [11].

HIV Testing. HIV-1 testing was performed using first the Determine rapid test (Abbot Diagnostics) [12]. If the sample was not reactive, it was considered HIV-negative. Otherwise, the Statpak rapid test (ChemoBio Diagnostics Systems) was used to confirm HIV positivity. In case of disagreement between the 2 tests, a tie-breaker test, the Unigold rapid test (Organics), was used. All HIV-positive results were subsequently confirmed by ELISA or PCR assay. Young women who were HIV-positive were referred to health institutions that offered treatment, care, and support services.

Syphilis testing. Syphilis testing was routinely performed for all women who attended the Naguru Teenage Information and Health Centre, by use of a commercially available, standard Rapid Plasma Reagin 18-mm Circle Card test (Quorum Diagnostics) Women with reactive Rapid Plasma Reagin test results were referred to established laboratories for confirmation of the results before treatment was offered.

Pregnancy testing. All young women were tested for pregnancy by use of a commercially available human chorionic gonadotropin dipstick pregnancy test (Cypress Diagnostics), and the results were communicated immediately to each woman.

Ethical issues. All study participants signed an informed consent form, or an assent form, if the individual was a minor, in accordance with the recommendations of the ethical review committees of the Faculty of Medicine, Makerere University; the Uganda National Council of Science and Technology; and the International Agency for Research on Cancer, which approved the study.

Statistical analysis. We used Stata (Stata) to compute odds ratios (ORs) and corresponding 95% confidence intervals (CIs)

for various characteristics using unconditional, multiple logistic regression models in which HPV infection was evaluated as the dependent variable. The ORs presented were adjusted for age group (≤ 18 years, 19–20 years, or 21–24 years), HIV infection status (negative, positive, or unknown) and lifetime number of sexual partners (1, 2, 3, or ≥ 4). We assessed the statistical significance of OR trends by considering the categorical variable as a continuous variable in the logistic model.

To estimate the proportion of young women who had probably already been infected by HPV 16 or 18 during single years of age between ≤ 16 and ≥ 21 , we first computed the age-specific prevalence of infection with HPV 16 or 18 and then estimated the cumulative incidence of infection with the same types, assuming a 1-year persistence rate of 30% [13]. For instance, the cumulative incidence of HPV 16 infection at any year of age was computed by adding the prevalence of infection with that HPV type in the year of age in question and in the previous year, minus the fraction of infections that were assumed to be carried over from one year to the next (i.e., 30%).

RESULTS

Of 1,646 eligible young women, 1,457 (88.5%) were interviewed and subsequently underwent pelvic examination and the collection of exfoliated cervical cells. One hundred eighty-two samples were inadequate as a result of contamination during transportation or because of mislabelling, which left 1,275 women available for the present analysis. The median age was 20 years (range, 12–24 years). The majority of the women (77%) had never been married, but 47% had been pregnant. Education level was rather high (77% reported at least secondary education). Eighty-one percent of the women were Christian and 19% were Muslim. Very few reported that they smoked cigarettes (2.5%) or had accepted money or gift in exchange for sexual intercourse (6.2%) (data not shown).

Of 1,275 women, 950 (75.0%) agreed to be tested for HIV; of these 950 women, 82 (8.6%) were HIV positive. Only 467 par-

ticipants were screened for syphilis because the test kit was unavailable during certain periods of the study. A total of 18 women (3.9%) were positive for syphilis.

Overall, 74.6% of our study participants were positive for 1 or more HPV types (table 1). High-risk types were found more often (51.4%), compared with low-risk types (39.8%). Among high-risk types, the most frequently detected were HPV 52 (13.2%), 51 (12.3%), 18 (10.7%), and 16 (10.6%); among low-risk types, HPV 6 (15.5%) and 11 (13.3%) predominated. Ninety-five women had samples that were HPV X positive at the first reverse hybridization assay, which then went through a second round of testing for 14 additional types. After this second round of testing, we determined that 57 of these women had infections that could be assigned to 1 or more specific types; the types most frequently detected were HPV 30 (9 women), 61 (9 women), and 67 (10 women). At the end of 2 rounds of testing, only 3.0% of all women, and 0% of HIV-positive women, could not be assigned any HPV type, and 521 (54.8%) of the HPV-positive women had multiple-type infections.

Study participants who were HIV positive showed higher a prevalence of HPV infection (87.8%), compared with HIV-negative subjects (73.2%) (table 1), and the largest difference was found with respect to multiple-type infections, which were detected in 37.3% of HIV-negative women and in 64.6% of HIV-positive women (figure 1). The mean number of HPV types detected in HPV-positive women without HIV infection was 2.1 (range, 1–10); in women with HIV infection, the mean number of types detected was 2.8 (range, 1–9) (*t* test, 3.88; *P* < .001). Figure 1 also shows the most frequent combinations of types detected in multiple-type infections. Among HIV-negative women, multiple-type infections most frequently included the combination of HPV 16 or 18 and other high-risk types (13.8% of women), whereas combinations of high-risk types that did not include HPV 16 or 18 predominated (22.0%) among HIV-positive women. Small percentages of women were affected only by HPV 16 and/or 18 or by low-risk types.

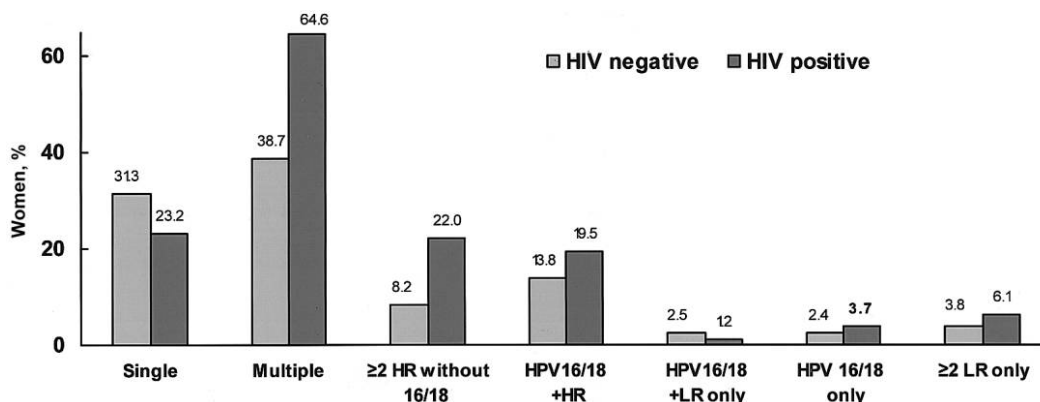


Figure 1. Multiple-type human papillomavirus (HPV) infections among 868 HIV-negative and 82 HIV-positive young women in Kampala, Uganda. Data includes the second round of HPV testing. HR, high-risk type; LR, low-risk type. HPV 16/18, HPV type 16 and/or 18

Table 1. Prevalence of human papillomavirus (HPV) types among 1,275 HPV-infected young women in Kampala, Uganda, by HIV infection status.

HPV type	Women, by infection type, no. (%)								
	HIV negative (n = 868)			HIV positive (n = 82)			Total ^a (n = 1,275)		
	Single HPV type	Multiple HPV types	Total	Single HPV type	Multiple HPV types	Total	Single HPV type	Multiple HPV types	Total
None	233 (26.8)	10 (12.2)	324 (25.4)
Any	311	324	635 (73.2)	19	53	72 (87.8)	446	505	951 (74.6)
High-risk type									
16	10	83	93 (10.7)	2	13	15 (18.3)	18	117	135 (10.6)
18	11	94	105 (12.1)	0	8	8 (9.8)	15	122	137 (10.7)
31	10	44	54 (6.2)	0	13	13 (15.9)	11	68	79 (6.2)
33	10	73	83 (9.6)	2	14	16 (19.5)	13	107	120 (9.4)
35	5	37	42 (4.8)	0	7	7 (8.5)	8	66	74 (5.8)
39	9	25	34 (3.9)	0	4	4 (4.9)	14	44	58 (4.5)
45	5	16	21 (2.4)	0	8	8 (9.8)	6	38	44 (3.5)
51	17	75	92 (10.6)	1	14	15 (18.3)	27	130	157 (12.3)
52	22	83	105 (12.1)	1	16	17 (20.7)	28	140	168 (13.2)
56	11	54	65 (7.5)	0	8	8 (9.8)	19	88	107 (8.4)
58	3	17	20 (2.3)	0	5	5 (6.1)	5	33	38 (3.0)
59	5	14	19 (2.2)	0	3	3 (3.7)	8	23	31 (2.4)
68/73	14	45	59 (6.8)	1	9	10 (12.2)	18	72	90 (7.1)
Subtotal	132	299	431 (49.7)	7	48	55 (67.1)	190	465	655 (51.4)
Low-risk type									
6	29	104	133 (15.3)	1	12	13 (15.9)	40	158	198 (15.5)
11	36	74	110 (12.7)	3	11	14 (17.1)	54	115	169 (13.3)
34	0	0	0	0	0	0	0	1	1 (0.1)
40	5	26	31 (3.6)	1	3	4 (4.9)	6	34	40 (3.1)
42	0	1	1 (0.1)	0	0	0	0	3	3 (0.2)
43	2	25	27 (3.1)	0	6	6 (7.3)	3	37	40 (3.1)
44	1	11	12 (1.4)	1	4	5 (6.1)	4	21	25 (2.0)
53	5	17	22 (2.5)	0	3	3 (3.7)	5	29	34 (2.7)
54	6	14	20 (2.3)	2	3	5 (6.1)	14	22	36 (2.8)
66	13	33	46 (5.3)	0	9	9 (11.0)	17	52	69 (5.4)
70	9	13	22 (2.5)	1	5	6 (7.3)	13	25	38 (3.0)
74	5	3	8 (0.9)	0	2	2 (2.4)	5	7	12 (0.9)
Subtotal	111	229	340 (39.2)	9	34	43 (52.4)	161	347	508 (39.8)
X ^b	68	-	68 (7.8)	3	-	3 (3.7)	95	-	95 (7.5)

NOTE. Percentages add up to more than the overall prevalence of HPV infection because of multiple-type infections.

^a Includes 325 young women whose HIV infection status was unknown.

^b Percentage of women with HPV X fell to 3.1%, 0% and 3.0% among HIV-negative, HIV-positive, and all women, respectively, after the second round of testing for HPV 26, 30, 55, 61, 62, 64, 67, 71, 82, 83, 84, 87, 89, and 90.

The distribution of HPV types among all infections (single type and multiple type) is shown in figure 2, according to HIV infection status. HPV 16 represented 7.2% of all infections in HIV-negative women and 7.5% of all infections in HIV-positive women. The distribution of other HPV types was also similar in the 2 groups of women, with the exception of HPV 18, which was underrepresented among HIV-positive women ($\chi^2_1 = 4.15$; $P = .042$).

Table 2 shows the association between HPV positivity and different characteristics after adjustment for HIV positivity,

age group, and lifetime number of sexual partners. A significant trend of decreasing HPV infection prevalence with increasing age emerged ($P < .004$). HPV positivity was significantly related to HIV infection status (OR, 2.4 [95% CI, 1.2–4.8]), employment in the tertiary sector (OR, 1.6 [95% CI, 1.1–2.2]), lifetime number of sexual partners (OR for ≥ 4 vs 1 partner, 2.2 [95% CI, 1.5–3.2]), a positive pregnancy test (OR, 1.7 [95% CI: 1.1–2.7]), and detection of genital warts at the study visit (OR, 2.0 [95% CI, 1.1–3.8]), but not to age at first sexual intercourse.

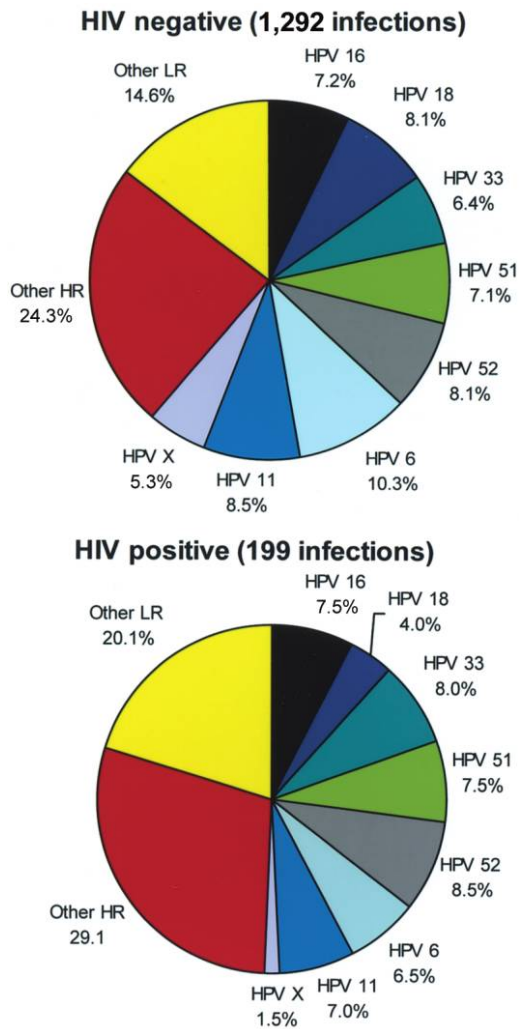


Figure 2. Distribution of human papillomavirus (HPV) infections among women in Kampala, Uganda according to infection type and HIV infection status. HR, high-risk type; LR, low-risk type.

Religion, education level, cigarette smoking status, marital status, parity, number of sexual partners in the last year, acceptance of money or gift in exchange for sexual intercourse, the use of hormonal contraceptives or condoms, and a history of sexually transmitted diseases were not significantly associated with HPV positivity (data not shown).

Figure 3 shows the age-specific prevalence and an estimate of cumulative incidence for infection with HPV 16 and 18. For each type, in no age group did the prevalence of infection exceed 15%. Cumulative incidence by age 18 was estimated to be 31.9% for HPV 16 infection and 27.0% for HPV 18 infection, and rose to approximately 50% for each type by age 21.

DISCUSSION

Our present study, to our knowledge the largest ever conducted among young women in Africa, showed that 3 out of 4 women

were HPV-positive, and half harbored high-risk HPV types. Multiple-type infections were more frequent than single-type infections, and seldom were HPV 16 or 18 not accompanied by other high-risk types.

HPV infection prevalences higher than 70% have so far been reported only in studies of HIV-positive women [2], but only 9% of the women in our study were HIV positive. A relatively high prevalence of HPV infection (between 25% and 40%) has

Table 2. Association between human papillomavirus (HPV) positivity and selected characteristics of 1,275 young women in Kampala, Uganda.

Characteristic	Women, no.	HPV DNA-positive, no. (%)	OR (95% CI) ^a	P for trend
Age				
12–16 years ^b	77	59 (76.6)	1	.004
17–18 years	285	227 (79.7)	1.2 (0.6–2.1)	
19–20 years	398	291 (73.1)	0.8 (0.4–1.3)	
21–22 years	328	241 (73.5)	0.7 (0.4–1.3)	
23–24 years	187	133 (71.1)	0.6 (0.3–1.1)	
HIV infection status				
Negative ^b	868	635 (73.2)	1	
Positive	82	72 (87.8)	2.4 (1.2–4.8)	
Unknown	325	244 (75.1)	1.0 (0.8–1.4)	
Occupation				
None and/or housewife ^b	719	525 (73.0)	1	
Manual workers	169	124 (73.4)	1.0 (0.7–1.4)	
Clerical workers	60	39 (65.0)	0.8 (0.4–1.4)	
Tertiary sector ^c	304	246 (80.9)	1.6 (1.1–2.2)	
Age at first sexual intercourse				
18–24 years ^b	380	267 (70.3)	1	.88
16–17 years	469	352 (75.1)	1.0 (0.7–1.4)	
<15 years	403	315 (78.2)	1.0 (0.7–1.5)	
Lifetime number of sexual partners				
1 ^b	324	221 (68.2)	1	<.001
2	398	295 (74.1)	1.4 (1.0–1.9)	
3	273	207 (75.8)	1.6 (1.1–2.3)	
>4	278	227 (81.7)	2.2 (1.5–3.2)	
Pregnancy test^d				
Negative ^b	1121	823 (73.4)	1	
Positive	151	125 (82.8)	1.7 (1.1–2.7)	
Genital warts^d				
No ^b	1172	862 (73.6)	1	
Yes	97	84 (86.6)	2.0 (1.1–3.8)	

NOTE. Figures do not add up to the total because of missing values. CI, confidence interval; OR, odds ratio.

^a Adjusted for age, HIV infection status, and lifetime number of sexual partners, as appropriate.

^b Reference category.

^c Includes women employed in shops, bars and restaurants.

^d At the time of gynecological examination.

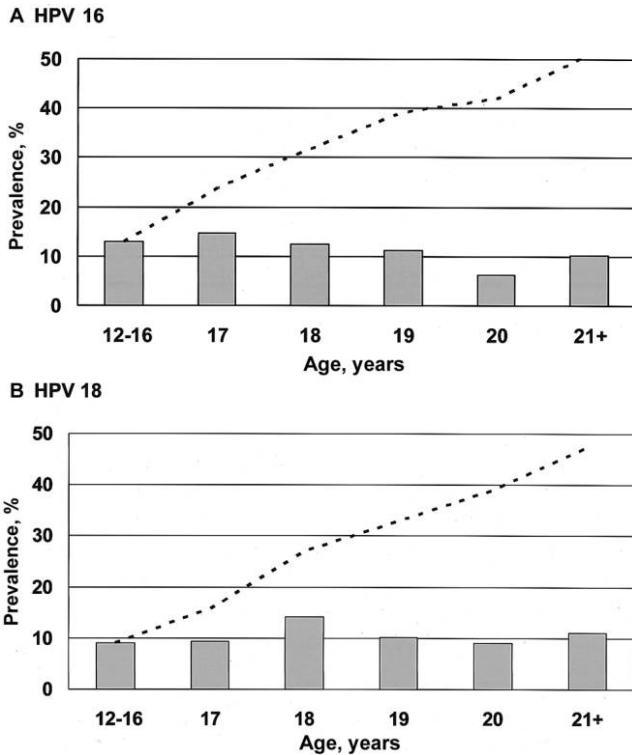


Figure 3. Prevalence and estimated cumulative incidence of infection with HPV 16 (A) and HPV 18 (B) among women in Kampala, Uganda, according to age. Data assumes a 1-year persistence rate of 30%.

been found in many studies from sub-Saharan Africa [14,15], notably in Eastern Africa [16–19], where the incidence of cervical cancer is reportedly higher than in Western Africa [1]. In the only previously published survey performed in Uganda, which was carried out in a rural area, Hybrid Capture 2 (Digene) was used to detect high-risk HPV types. The prevalence of infection with high-risk HPV types among women aged 15–29 years was 22% among 395 HIV-negative women and 52% among 71 HIV-positive women (i.e., lower than in our present study). Conversely, in that study, the prevalence of HIV infection among young women (18.0%) [6] was higher than that observed in our clinic-based sample from Kampala. Because of the varying study designs, particularly with respect to the age range of study subjects and the HPV testing protocols, differences in prevalence should be interpreted with caution, and it is worth bearing in mind that the PCR assay that we used in our study has a higher sensitivity than Hybrid Capture 2 and some other PCR-based assays [20].

HPV infection, because of its high prevalence and high transmissibility [21], tends to be acquired very early after sexual debut. Previous studies of young women have shown a very high prevalence of HPV infection, much higher than that among older women in the same areas, in the years immediately following first sexual intercourse. The prevalence of HPV infection was 54.5% among HIV-negative girls aged 13–21 years in San Fran-

cisco, California [4]; the prevalence was 39.9% in young women aged 20–24 years in Manchester, United Kingdom [22]; and 26.1% in young women younger than 20 years who attended an adolescent clinic in Bogota, Colombia [23]. Very high cumulative incidences were also reported, for example, an incidence of 44% after 3-year follow-up among young women aged 15–19 in Birmingham, United Kingdom [24]; and an incidence of 32% after 2-year follow-up among female university students aged 18–20 years in Washington [25].

In keeping with the concept of the rapid acquisition of HPV infection after first sexual intercourse in many different populations, we also found an inverse association between the prevalence of HPV infection and age, even in our very young study subjects. The strongest risk factors for HPV positivity were self-reported lifetime number of sexual partners and positivity for certain objective measurements made during the enrolment examination, (i.e., HIV positivity, the presence of genital warts, and pregnancy). Condom use did not seem related to HPV positivity, which is not surprising, as consistent use of this contraceptive method was rarely reported among our study population, and, by and large, it has been suggested that condoms confer at best partial protection against HPV transmission [26].

One of the main aims of the present study was to explore the distribution of different HPV types. In keeping with previous work on HPV types in different populations [27, 28], the proportion of HPV infection due to HPV 16 seemed to be lower among young women in Uganda, compared with populations outside sub-Saharan Africa. Among high-risk types, HPV 18, 51, and 52 were detected slightly more frequently than HPV 16, as were low-risk types HPV 6 and 11. All HPV types except HPV 18 were detected more often in HIV-positive women than in HIV-negative women. In keeping with the results of a large meta-analysis [2], the most striking difference we found was a much higher frequency of multiple-type HPV infections among HIV-positive women, compared with HIV-negative women. In addition, in the present study, a larger proportion of infection with multiple high-risk types in HIV-positive women included neither HPV 16 nor 18.

The HPV vaccines that are currently available have demonstrated activity only in the prevention of infection before exposure to the types included in the vaccine [29, 30]. Therefore, for optimal efficacy, HPV vaccination is recommended for girls aged 9–12 years [31]. The costs and barriers of reaching 9–12-year-old girls, however, may be substantial, especially in some low-resource countries. We, therefore, tried to explore the theoretical efficacy of relatively late delivery of a prophylactic HPV vaccine. Based on the actual prevalence of HPV infection, $\geq 85\%$ of women were negative for at least 1 of the 2 most oncogenic HPV types, HPV 16 or 18, at any year of age between 16 and 21 years. This may be, however, an overly optimistic assumption, as HPV positivity at any moment in time reflects only current viral shedding and is not an accurate measure of overall exposure

[31]. Our attempt to estimate cumulative incidence must be interpreted with great caution, as it is derived from prevalence in a cross-sectional study, rather than from incidence rates in a prospective study. Our estimates suggest, however, that up to approximately age 18, as much as 70% of women may still benefit from prophylactic vaccines against at least 1 of the 2 most oncogenic HPV types. Our estimates of the cumulative incidence of HPV infection were relatively robust to the assumption of 12-month persistence in the 10%–40% range shown by different cohort studies [13, 32, 33].

In conclusion, our study of young women who attended a clinic for teenagers in Kampala, Uganda, revealed an extremely elevated prevalence of HPV infection in HIV-positive and HIV-negative young women. The large size of the study, the very few refusals to participate, and the use of highly sensitive PCR-based assays strengthen the validity of our findings. Clinics such as the one in our study may contribute to the catching up of unvaccinated young women who have recently become sexually active. In addition, clinics for teenagers would certainly represent ideal places to set up sentinel surveys to monitor the early effects of large-scale vaccination on protection against HPV in low-resource countries [34].

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References

- Parkin DM, Ferlay J, Hamdi-Cherif M, et al. Cancer in Africa: epidemiology and prevention. Lyon: IARC Press, 2003.
- Clifford GM, Gonçalves MA, Franceschi S, HPV and HIV Study Group. Human papillomavirus types among women infected with HIV: a meta-analysis. *AIDS* 2006; 20:2337–44.
- Palefsky JM, Holly EA. Chapter 6: Immunosuppression and coinfection with HIV. *J Natl Cancer Inst Monogr* 2003; 41–6.
- Moscicki AB, Ellenberg JH, Vermund SH, et al. Prevalence of and risks for cervical human papillomavirus infection and squamous intraepithelial lesions in adolescent girls: impact of infection with human immunodeficiency virus. *Arch Pediatr Adolesc Med* 2000; 154:127–34.
- PATH. Cervical cancer vaccine. Available at: http://www.path.org/projects/cervical_cancer_vaccine.php. Accessed on 19 December 2007.
- Serwadda D, Wawer MJ, Shah KV, et al. Use of a hybrid capture assay of self-collected vaginal swabs in rural Uganda for detection of human papillomavirus. *J Infect Dis* 1999; 180:1316–9.
- Sankaranarayanan R, Basu P, Wesley RS, et al. Accuracy of visual screening for cervical neoplasia: results from an IARC multicentre study in India and Africa. *Int J Cancer* 2004; 110:907–13.
- Sellers JW, Sankaranarayanan R. Colposcopy and treatment of cervical intraepithelial neoplasia: a beginner's manual. Lyon: International Agency for Research on Cancer, 2003.
- Kleter B, van Doorn LJ, ter Schegget J, et al. Novel short-fragment PCR assay for highly sensitive broad-spectrum detection of anogenital human papillomaviruses. *Am J Pathol* 1998; 153:1731–9.
- Kleter B, van Doorn LJ, Schrauwen L, et al. Development and clinical evaluation of a highly sensitive PCR-reverse hybridization line probe assay for detection and identification of anogenital human papillomavirus. *J Clin Microbiol* 1999; 37:2508–17.
- Muñoz N, Bosch FX, Castellsagué X, et al. Against which human papillomavirus types shall we vaccinate and screen? The international perspective. *Int J Cancer* 2004; 111:278–85.
- Downing RG, Otten RA, Marum E, et al. Optimizing the delivery of HIV counseling and testing services: the Uganda experience using rapid HIV antibody test algorithms. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; 18:384–8.
- Molano M, van den Brule AJ, Plummer M, et al. Determinants of clearance of human papillomavirus infections in Colombian women with normal cytology: a population-based, 5-year follow-up study. *Am J Epidemiol* 2003; 158:486–94.
- Thomas JO, Herrero R, Omigbodun AA, et al. Prevalence of papillomavirus infection in women in Ibadan, Nigeria: a population-based study. *Br J Cancer* 2004; 90:638–45.
- Clifford GM, Franceschi S. HPV in sub-Saharan Africa. *Papillomavirus Report* 2005; 16:322–6.
- Castellsagué X, Menendez C, Loscertales MP, et al. Human papillomavirus genotypes in rural Mozambique. *Lancet* 2001; 358:1429–30.
- Mayaud P, Gill DK, Weiss HA, et al. The interrelation of HIV, cervical human papillomavirus, and neoplasia among antenatal clinic attenders in Tanzania. *Sex Transm Infect* 2001; 77:248–54.
- De Vuyst H, Steyaert S, Van Renterghem L, et al. Distribution of human papillomavirus in a family planning population in Nairobi, Kenya. *Sex Transm Dis* 2003; 30:137–42.
- Baay MF, Kjetland EF, Ndhlovu PD, et al. Human papillomavirus in a rural community in Zimbabwe: the impact of HIV co-infection on HPV genotype distribution. *J Med Virol* 2004; 73:481–5.
- Iftner T, Villa LL. Chapter 12: Human papillomavirus technologies. *J Natl Cancer Inst Monogr* 2003; 80–8.
- Burchell AN, Richardson H, Mahmud SM, et al. Modeling the sexual transmissibility of human papillomavirus infection using stochastic computer simulation and empirical data from a cohort study of young women in Montreal, Canada. *Am J Epidemiol* 2006; 163:534–43.
- Kitchener HC, Almonte M, Wheeler P, et al. HPV testing in routine cervical screening: cross sectional data from the ARTISTIC trial. *Br J Cancer* 2006; 95:56–61.
- Molano M, Posso H, Weiderpass E, et al. Prevalence and determinants of HPV infection among Colombian women with normal cytology. *Br J Cancer* 2002; 87:324–33.
- Woodman CB, Collins S, Winter H, et al. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. *Lancet* 2001; 357:1831–6.
- Winer RL, Lee SK, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. *Am J Epidemiol* 2003; 157:218–26.
- Manhart LE, Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. *Sex Transm Dis* 2002; 29:725–35.
- Clifford GM, Gallus S, Herrero R, et al. Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis. *Lancet* 2005; 366:991–8.
- de Sanjosé S, Diaz M, Castellsagué X, et al. Worldwide prevalence and genotype distribution of cervical HPV DNA in 157,897 women with normal cytology: a meta-analysis of 78 studies. *Lancet Infect Dis* 2007; 7:453–9.
- Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med* 2007; 356:1928–43.

30. Paavonen J, Jenkins D, Bosch FX, et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. *Lancet* **2007**; 369:2161–70.
31. Saslow D, Castle PE, Cox JT, et al. American Cancer Society Guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. *CA Cancer J Clin* **2007**; 57:7–28.
32. Giuliano AR, Harris R, Sedjo RL, et al. Incidence, prevalence, and clearance of type-specific human papillomavirus infections: the Young Women's Health Study. *J Infect Dis* **2002**; 186:462–9.
33. Schiffman M, Herrero R, Desalle R, et al. The carcinogenicity of human papillomavirus types reflects viral evolution. *Virology* **2005**; 337:76–84.
34. Dillner J, Arbyn M, Dillner L. Translational mini-review series on vaccines: monitoring of human papillomavirus vaccination. *Clin Exp Immunol* **2007**; 148:199–207.