

## HUMAN PAPILLOMAVIRUS INFECTION IN WOMEN INFECTED WITH THE HUMAN IMMUNODEFICIENCY VIRUS

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**ABSTRACT**

**Background** Among women infected with the human immunodeficiency virus (HIV), there is a high prevalence of human papillomavirus (HPV) infections. However, little is known about the natural history of HPV infections in HIV-seropositive women, and persistent HPV infections may explain the increased risk of cervical squamous intraepithelial lesions and invasive cervical cancer in HIV-seropositive women.

**Methods** A total of 220 HIV-seropositive and 231 HIV-seronegative women in the New York City area were evaluated at two or more semiannual gynecologic examinations that included a Pap test, a test for HPV DNA, and colposcopy.

**Results** HPV DNA was detected at the initial examination in 56 percent of the HIV-seropositive and 31 percent of the HIV-seronegative women. After four examinations, the cumulative prevalence of HPV infection was 83 percent in the seropositive women and 62 percent in the seronegative women ( $P < 0.001$ ). Persistent HPV infections were found in 24 percent of the seropositive women but in only 4 percent of the seronegative women ( $P < 0.001$ ). Twenty percent of the seropositive women and 3 percent of the seronegative women had persistent infections with HPV-16-associated viral types (16, 31, 33, 35, or 58) or HPV-18-associated types (18 or 45) ( $P < 0.001$ ), which are most strongly associated with cervical cancer. The detection of HPV DNA in women with previously negative tests was not associated with sexual activity during the interval since the preceding examination.

**Conclusions** HIV-seropositive women have a high rate of persistent HPV infections with the types of HPV that are strongly associated with the development of high-grade squamous intraepithelial lesions and invasive cervical cancer. These persistent infections may explain the increased incidence of squamous intraepithelial lesions in HIV-seropositive women. (N Engl J Med 1997;337:1343-9.)

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**I**NFECTION with the human immunodeficiency virus (HIV) is an important risk factor for human papillomavirus (HPV) infection and the development of HPV-associated lesions in the female genital tract. HPV DNA is 2 to 3 times as frequent in cervicovaginal-lavage specimens and almost 15 times as common in anal-swab specimens from HIV-seropositive women as in those from HIV-seronegative women.<sup>1-6</sup> In addition, HIV-seropositive

women are about five times as likely as HIV-seronegative women to have squamous intraepithelial lesions, vulvovaginal condyloma acuminata, or anal intraepithelial neoplasia.<sup>2-8</sup> These findings suggest that HIV infection, HIV-associated immunosuppression, or both increase a woman's susceptibility to HPV infection or alter the natural history of preexisting HPV infection.

In HIV-seronegative women, the majority of anogenital HPV infections appear to be transient and self-limited.<sup>9</sup> Persistent infection with certain types of HPV, such as types 16, 18, 31, 33, 35, and 45, is thought to be necessary for the development of high-grade squamous intraepithelial lesions and cervical cancer.<sup>10</sup> Since HIV-seropositive women have an increased prevalence of squamous intraepithelial lesions, we suspect that these women are at increased risk for persistent HPV infection. However, most studies of anogenital HPV infections in HIV-seropositive women have been cross-sectional in design, and information about persistence and other aspects of the natural history of HPV infections in HIV-seropositive women is limited.

We conducted a prospective cohort study to determine the gynecologic characteristics associated with HIV infection. Women enrolled in this study underwent periodic HPV DNA testing, which enabled us to examine the effects of HIV infection and HIV-associated immunosuppression on the natural history of HPV infection.

**METHODS****Study Design**

A total of 424 HIV-seropositive and 381 HIV-seronegative women were recruited from the New York City area during the period from 1991 through 1993. The cohort is described in detail elsewhere.<sup>17</sup> In brief, women were recruited from clinics for sexually transmitted diseases, methadone maintenance, and HIV infection and from a study of HIV transmission in couples. Women were enrolled without regard to their risk of HPV infection or the clinical status of those infected with HIV. Informed consent was obtained from all the women enrolled, and the study was ap-

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proved by the institutional review boards of all the participating institutions.

At enrollment and at approximately six-month intervals thereafter, participants were interviewed and underwent a gynecologic examination that included a Pap test, a cervicovaginal lavage of 10 ml of phosphate-buffered saline (pH 7.4), and colposcopy with biopsy, if indicated. The current analysis is restricted to women without squamous intraepithelial lesions on the initial examination who had HPV tests at two or more examinations within a 12-month period. CD4+ T-lymphocyte counts within six months of each examination were obtained from clinic records or were obtained specifically for the study.

#### Detection of HPV DNA

Polymerase-chain-reaction (PCR) tests for HPV DNA were performed in a blinded fashion. Genomic DNA was isolated from cervicovaginal-lavage specimens<sup>1</sup> and amplified with the use of both the HPV L1 consensus primers of Manos et al., which amplify 25 types of anogenital HPV,<sup>11</sup> and type-specific E6 primers for HPV 16 and 18.<sup>12</sup> Samples were defined as positive for HPV DNA if they contained an ethidium bromide-stained band of the correct molecular weight after amplification and polyacrylamide-gel electrophoresis. The HPV type was determined by analysis of restriction-fragment-length polymorphism of the L1 PCR product.<sup>13</sup> In some cases, L1 PCR products could not be typed in this manner because too many types of HPV were present (in 3 percent of the samples) or there was too little amplification product (in 12 percent). Type-specific PCR for HPV types 16 and 18 detected considerably more infections with HPV types 16 and 18 than did the L1 PCR; 46 of 101 HPV-16 infections (46 percent) and 66 of 92 HPV-18 infections (72 percent) were detected only with the type-specific E6 primers. In contrast, only 24 of 101 HPV-16 infections (24 percent) and 7 of 92 HPV-18 infections (8 percent) were detected only with the L1 method.

Samples that were negative for HPV DNA were amplified with primers for the *cKi-ras* gene to ensure the integrity of the samples.<sup>12</sup> Samples in which neither HPV DNA nor the *cKi-ras* gene was amplified were considered inadequate for analysis and were excluded.

#### Statistical Analysis

The cumulative prevalence of HPV infection, defined as the cumulative probability of a positive test for HPV DNA at each sequential examination, was estimated with the use of the Kaplan-Meier method and the log-rank test.<sup>14</sup> Cumulative-prevalence curves were calculated according to the time to the first positive HPV test. In all Kaplan-Meier estimates, missing examinations were ignored.

Among women with detectable HPV DNA of any type at the initial examination, the probability of positive HPV tests at subsequent visits was estimated with the use of the Kaplan-Meier method and the log-rank test. These curves were calculated according to the time to the first negative HPV test. However, this approach does not differentiate among the specific types of HPV that are shed, and different types could be shed at different times. Therefore, we also examined persistent HPV infections, defined as the detection of the same type of HPV at two or more examinations during a period of 3 to 12 months. To compare the percentages of HIV-seropositive and HIV-seronegative women with persistent HPV infections, odds ratios and confidence intervals were calculated from logistic-regression models,<sup>15</sup> which were adjusted for the number of examinations by using indicator variables for two, three, four, five, or six or more examinations.

New HPV infections were analyzed among the women with no HPV detected on two or more consecutive examinations. The rate of new infections was defined as the number of newly detected HPV infections after two or more negative tests, divided by the number of examinations until an infection was detected or, if no infection was detected, the end of follow-up. For women with new HPV infections, information about sexual behavior during the in-

terval between the examination at which HPV was first detected and the preceding examination was analyzed, and for women with no new infections, information about sexual practices during the interval between the last two examinations was analyzed.

## RESULTS

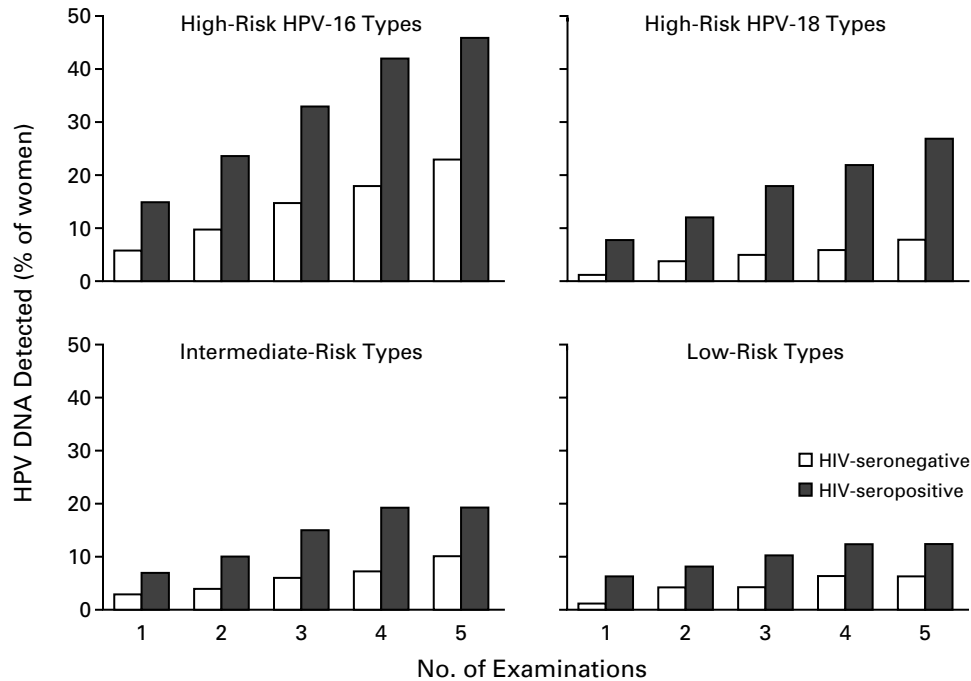
### Sociodemographic Characteristics of the Cohort

The cohort was composed of 424 HIV-seropositive and 381 HIV-seronegative women, of whom 220 HIV-seropositive and 231 HIV-seronegative women were included in the analysis. The two reasons for exclusion from the analysis were that cervical disease was detected at the initial examination (in 104 HIV-seropositive and 24 HIV-seronegative women) and that results were unavailable for two HPV tests within a 12-month interval during the study period (in 100 HIV-seropositive and 126 HIV-seronegative women). The women who were excluded from the analysis because they had fewer than two HPV tests did not differ significantly from those included in the analysis in age, race or ethnic group, education, marital status, or detection of HPV DNA at the initial examination ( $P > 0.05$  for all comparisons). However, women with two or more HPV tests were less likely to report a history of injection-drug use than those with fewer than two HPV tests (35 percent vs. 45 percent,  $P = 0.01$ ). Data from a total of 787 examinations in HIV-seropositive women and 721 in HIV-seronegative women were included in the analysis.

Among the women included in the analysis, those who were HIV-seropositive were similar to those who were HIV-seronegative in terms of age, race or ethnic group, education, and income. The mean age in both groups was 35 years. Forty percent of the seropositive women and 46 percent of the seronegative women were black ( $P = 0.13$ ), 45 percent of the seropositive women and 37 percent of the seronegative women had not completed high school ( $P = 0.07$ ), and 63 percent of each group had an annual income of less than \$10,000. The seropositive and seronegative women were similar in terms of the reported number of lifetime sexual partners, condom use, and age at first sexual intercourse. However, there were some differences in other characteristics. For example, 27 percent of the seropositive women and 39 percent of the seronegative women were married ( $P = 0.03$ ), 24 percent of the seropositive women and 16 percent of the seronegative women reported a history of prostitution ( $P = 0.05$ ), and 40 percent of the seropositive women and 31 percent of the seronegative women reported sexual abstinence during the month before the initial examination ( $P = 0.04$ ).

### Cumulative Prevalence of HPV DNA

HPV DNA was detected at the initial examination in 56 percent of the HIV-seropositive women and 31 percent of the HIV-seronegative women. The



**Figure 1.** Kaplan–Meier Estimates of the Cumulative Prevalence of Types of HPV DNA in 220 HIV-Seropositive Women and 231 HIV-Seronegative Women.

The high-risk HPV-16–associated types were 16, 31, 33, 35, and 58, the high-risk HPV-18–associated types were 18 and 45; the intermediate-risk types were 51 and 53; and the low-risk types were 6, 11, 43, and 44.

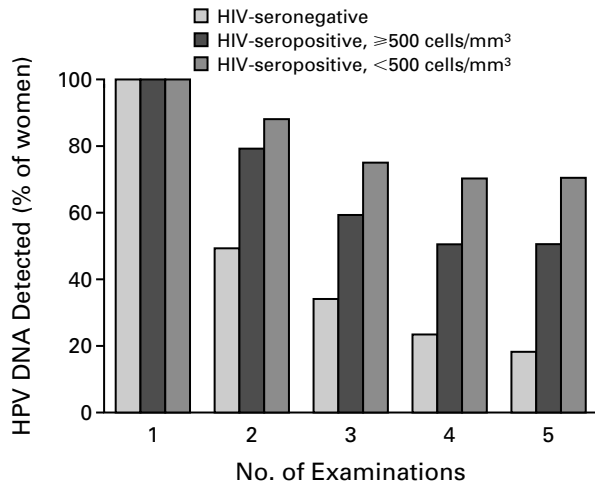
cumulative prevalence of HPV DNA was higher in the HIV-seropositive women than in the HIV-seronegative women ( $P < 0.001$  by the log-rank test) and was inversely related to the CD4+ T-lymphocyte count. For example, the cumulative HPV prevalence after four examinations was 62 percent in the seronegative women, 74 percent in the seropositive women with CD4+ counts of 500 or higher per cubic millimeter, and 95 percent in the seropositive women with CD4+ counts that were below 500 per cubic millimeter.

The cumulative prevalence of specific phylogenetic groupings of HPV types was also analyzed.<sup>16</sup> Figure 1 shows the cumulative prevalence of the high-risk HPV-16–associated types (16, 31, 33, 35, and 58), the high-risk HPV-18–associated types (18 and 45), the intermediate-risk types (51 and 53), and the low-risk types (6, 11, 43, and 44). The cumulative prevalence of each group of HPV types was higher in the HIV-seropositive women ( $P < 0.001$  for both groups of high-risk types,  $P = 0.002$  for the intermediate-risk types, and  $P = 0.02$  for the low-risk types, by the log-rank test).

HPV-16–associated types and HPV-18–associated types are of particular interest because they are strongly associated with high-grade squamous intraepithelial lesions and invasive cancer in women in the general population. At the initial examination, the prevalence

of HPV-16–associated types was 6 percent (95 percent confidence interval, 3 to 10 percent) in the seronegative women and 15 percent (95 percent confidence interval, 10 to 19 percent) in the seropositive women, and the prevalence of HPV-18–associated types was 1 percent (95 percent confidence interval, 0 to 3 percent) in the seronegative women and 7 percent (95 percent confidence interval, 3 to 10 percent) in the seropositive women. After four examinations, the cumulative prevalences in the seronegative and seropositive women were 18 percent (95 percent confidence interval, 13 to 24 percent) and 42 percent (95 percent confidence interval, 35 to 50 percent) for HPV-16–associated types and 6 percent (95 percent confidence interval, 3 to 9 percent) and 22 percent (95 percent confidence interval, 16 to 28 percent) for HPV-18–associated types, respectively.

Women who were positive for HPV at the initial examination frequently became negative for HPV during follow-up. Figure 2 shows the probability of detecting HPV DNA at subsequent examinations in women with detectable HPV at the initial examination. HIV-seropositive women were more likely than HIV-seronegative women to have positive HPV tests during subsequent examinations ( $P < 0.001$ ), and HIV-seropositive women with CD4+ T-lymphocyte counts of less than 500 per cubic millimeter were more likely than those with CD4+ counts of 500 or



**Figure 2.** Kaplan–Meier Estimates of the Probability of Persistent HPV Infection at Subsequent Examinations among Women with Detectable HPV at the Initial Examination, According to HIV Status and According to the CD4+ Count among HIV-Seropositive Women.

more per cubic millimeter to have positive HPV tests during subsequent examinations ( $P < 0.001$ ).

**Persistence of HPV Infection**

Persistent infection with a high-risk type of HPV may be necessary for the development of high-grade squamous intraepithelial lesions and invasive cervical cancer. We defined persistent infection as the detection of the same type of HPV at two or more examinations during a period of 3 to 12 months. HIV-seropositive women were more likely to have

persistent HPV infections than HIV-seronegative women (24 percent vs. 4 percent,  $P < 0.001$ ) (Table 1). Among the seropositive women, 19 percent with CD4+ counts of 500 or more per cubic millimeter, 24 percent with counts of 200 to 499 per cubic millimeter, and 33 percent with counts of less than 200 per cubic millimeter had persistent HPV infections ( $P = 0.23$ ) (Table 2).

Fourteen percent of the HIV-seropositive women and 3 percent of the HIV-seronegative women had persistent infections with HPV-16–associated viral types ( $P = 0.004$ ) (Table 1). Persistent infections with HPV-18–associated viral types were found in 8 percent of the HIV-seropositive women but in none of the HIV-seronegative women. Overall, infections with high-risk HPV types (those associated with HPV-16 or HPV-18) were persistent in 20 percent of the seropositive women and 3 percent of the seronegative women ( $P < 0.001$ ). The proportions of women who had persistent infections with other HPV types were also higher in the seropositive group than in the seronegative group. However, the distribution of HPV types was similar in the two groups, and HPV-16–associated types were the most common in both. Figure 3 shows the pattern of HPV shedding in the women with persistent HPV-16 infections. Although HPV detection varies from examination to examination, most women with persistent HPV-16 infections shed some type of HPV DNA at almost every examination.

**Risk Factors for Persistent HPV Infection**

In the univariate analysis, in which we controlled for the number of examinations, factors significantly associated with persistent HPV infection were HIV

**TABLE 1.** PERSISTENT HPV INFECTIONS AMONG WOMEN WITHOUT SQUAMOUS INTRAEPITHELIAL LESIONS AT THE INITIAL EXAMINATION, ACCORDING TO HPV TYPE AND HIV SEROLOGIC STATUS.\*

HPV TYPE	HIV-SEROPOSITIVE WOMEN (N=220)		HIV-SERONEGATIVE WOMEN (N=231)	
	PERSISTENT HPV INFECTION	RATIO OF PERSISTENT INFECTION TO ANY INFECTION†	PERSISTENT HPV INFECTION	RATIO OF PERSISTENT INFECTION TO ANY INFECTION†
	%	no. persistent/ no. any (%)	%	no. persistent/ no. any (%)
High risk				
HPV-16–associated (16, 31, 33, 35, or 58)	14.1	31/86 (36.0)	3.0	7/38 (18.4)
HPV-18–associated (18 or 45)	8.2	18/47 (38.3)	0	0/13
Intermediate risk (51 or 53)	6.4	14/36 (38.9)	0.9	2/16 (12.5)
Low risk (6, 11, 43, or 44)	1.8	4/25 (16.0)	0.4	1/12 (8.3)
Any of the above	24.1	53/123 (43.1)	3.9	9/58 (15.5)
Novel	8.6	19/80 (23.8)	3.9	9/45 (20.0)

\*A persistent infection was defined as the detection of the same type of HPV at two or more consecutive examinations during a period of 3 to 12 months.

†The ratio was calculated as the number of women with the specific type of HPV detected at two or more examinations during a period of 3 to 12 months divided by the number of women in whom the HPV type was ever detected.

seropositivity, a CD4+ count of less than 200 cells per cubic millimeter, less than 12 years of education, and a history of injection-drug use (Table 2). Unmarried women were more likely to have persistent HPV infections than married women. In the multivariate analysis, after adjustment for age, race or ethnic group, education, marital status, history of prostitution, history of injection-drug use, condom use, smoking, and history of cervical disease, HIV-seropositive women with CD4+ counts of less than 500 per cubic millimeter and those with counts of 500 or more per cubic millimeter were more likely to have persistent HPV infections than HIV-seronegative women. Being unmarried and having a history of injection-drug use remained significantly associated with persistent infection in the multivariate model with all the above-listed risk factors.

**New HPV Infections**

Forty-eight of 151 women (32 percent) who had negative HPV tests at the first and second examinations had detectable HPV at a subsequent examination. The rate of new infections among the women with initially negative HPV tests was 11 per 100 examinations in the HIV-seropositive group and 9 per 100 examinations in the HIV-seronegative group. The detection of new HPV infections in women with previously negative HPV tests was not associated with serologic status or with sexual activity since the preceding examination. The detection rate was 9 per 100 examinations among the women who reported no sexual activity since the prior examination, 9 per 100 examinations among those who reported intercourse with consistent use of condoms, and 12 per 100 examinations among those who reported intercourse with intermittent or no use of condoms (P=0.72). Among the women who became positive for HPV after two consecutive negative tests, 9 of 21 who were HIV-seropositive (43 percent) and 5 of 27 who were HIV-seronegative (19 percent) reported no sexual activity since the preceding examination.

**DISCUSSION**

HIV seropositivity and HIV-induced immunosuppression are known to be associated with an increased prevalence of anogenital HPV infections in men and women.<sup>1-7</sup> This association involves HPV infections of all types, as well as infections with multiple types of HPV, including those associated with neoplasia, such as HPV-16 and HPV-18. The increased prevalence of these infections suggests that HIV-seropositive women are at increased risk for squamous intraepithelial lesions and invasive cancer of the cervix, vagina, vulva, anus, and perianal region. HIV-associated alterations in the natural history of HPV infection may also influence the risk of HPV-associated disease in HIV-seropositive women.

**TABLE 2.** PERSISTENT HPV INFECTIONS AMONG WOMEN WITHOUT SQUAMOUS INTRAEPITHELIAL LESIONS AT THE INITIAL EXAMINATION, ACCORDING TO SOCIODEMOGRAPHIC CHARACTERISTICS AND POTENTIAL RISK FACTORS FOR HPV INFECTION.

VARIABLE	No. OF WOMEN*	PERSISTENT HPV INFECTION†	ODDS RATIO (95% CI)‡
		%	
HIV status			
Seropositive	220	24.1	7.5 (3.6-16)
Seronegative	231	3.9	1.0
CD4+ count in HIV-seropositive women			
<200/mm <sup>3</sup>	42	33.3	2.8 (1.1-6.8)
200-499/mm <sup>3</sup>	74	24.3	1.1 (0.48-2.4)
≥500/mm <sup>3</sup>	73	19.2	1.0
Age			
<29 yr	98	17.3	1.1 (0.48-2.3)
30-39 yr	230	10.9	0.6 (0.31-1.2)
≥40 yr	122	15.6	1.0
Race or ethnic group			
Non-Hispanic black	197	14.2	1.1 (0.51-2.2)
Hispanic	130	14.6	1.2 (0.52-2.5)
Non-Hispanic white	113	11.5	1.0
Marital status			
Married	147	6.8	0.3 (0.14-0.66)
Unmarried	304	16.8	1.0
Education			
<12 yr	185	15.7	1.5 (0.83-2.7)
≥12 yr	264	12.1	1.0
Smoking status			
Current smoker	299	14.0	1.3 (0.70-2.5)
Nonsmoker	152	13.2	1.0
Use of injection drugs			
Yes	159	18.9	2.7 (1.3-4.3)
No	291	10.7	1.0
History of prostitution			
Yes	91	13.2	0.9 (0.42-1.9)
No	359	13.6	1.0
History of cervical disease			
Yes	34	23.5	1.9 (0.74-3.4)
No	417	12.9	1.0

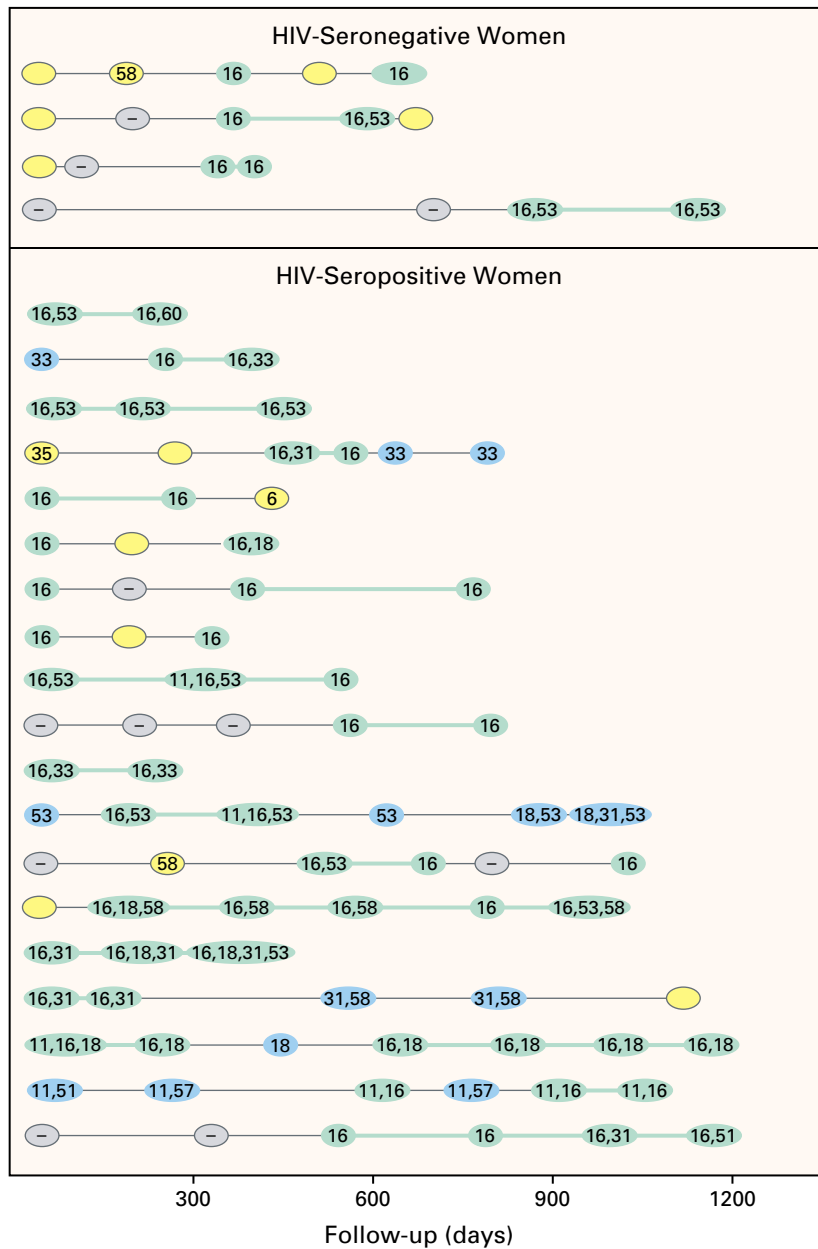
\*For some variables, numbers do not add up to totals because of missing data.

†A persistent infection was defined as the detection of the same type of HPV at two or more examinations during a period of 3 to 12 months.

‡Odds ratios and 95 percent confidence intervals were calculated by logistic-regression analysis for each variable separately, with adjustment for the number of examinations as an indicator variable. CI denotes confidence interval.

In women in the general population, the shedding of HPV from the lower genital tract is highly variable, and several studies have shown that persistent shedding of high-risk types of HPV is an important factor in the development of squamous intraepithelial lesions of the cervix.<sup>9</sup> If HIV infection causes persistent HPV shedding, this effect may promote the development of anogenital squamous intraepithelial lesions and cancers in HIV-seropositive women.

In our study, we found that HPV shedding was highly variable in both HIV-seropositive and HIV-seronegative women. Of the women examined three or more times, only 49 percent in the HIV-seropos-



**Figure 3.** Patterns of HPV Detection in Women with Persistent HPV-16 Infections.

Four HIV-seronegative and 19 HIV-seropositive women had persistent infections with HPV-16. Each woman is represented by a horizontal line, and each examination by a colored circle or oval. Green circles represent the detection of HPV-16; blue circles the detection of an HPV type other than HPV-16 that was identified at least twice in the same patient; yellow circles the detection of HPV that could not be typed or was a type detected only once in the patient; and gray circles undetectable HPV.

itive group and 42 percent in the HIV-seronegative group were consistently positive or negative for HPV at all examinations. In many women, several different HPV types were detected at different examinations. Therefore, studies that have tested HIV-seropositive women for HPV infections on a single

occasion may have considerably underestimated the prevalence of such infections. In our study, the cumulative prevalence of infection with any type of HPV after four examinations (during approximately two years of follow-up) was 95 percent in the HIV-seropositive women with CD4+ counts of less than

500 per cubic millimeter and 74 percent in those with CD4+ counts of 500 or more per cubic millimeter. After four examinations, the cumulative prevalences of infection with HPV-16 and HPV-18, high-risk "oncogenic" types of HPV, were 21 percent and 22 percent, respectively, in HIV-seropositive women. These cumulative prevalences, which are considerably higher than the point prevalences in our previous study,<sup>7</sup> indicate that most HIV-seropositive women have cervicovaginal HPV infections and that a large proportion of these women are infected with high-risk types of HPV.

Few studies have determined the cumulative prevalence of anogenital HPV infections in women in the general population. In a study of predominantly white middle-class women with normal cervical cytologic findings, 26 percent had HPV in cervicovaginal-lavage specimens, detected with a PCR assay, at the first visit.<sup>17</sup> After two visits, the cumulative prevalence was 36 percent.<sup>17</sup> Similarly, in a population-based study of 276 young women in Sweden, HPV DNA was detected in 21 percent of the women at the initial visit, and the cumulative prevalence was 25 percent after two examinations, with the use of a nested-PCR method to amplify HPV DNA from cervical scrapings.<sup>18</sup>

Persistent infection with high-risk types of HPV appears to have a central role in the development of squamous intraepithelial lesions and invasive cervical cancer. In a cohort of women with abnormal cervical cytologic findings, Ho et al. found that persistent infection with specific types of HPV resulted in chronic cervical dysplasia.<sup>19</sup> However, little is known about the persistence of HPV infection, or about the relation between persistent infection and the development of squamous intraepithelial lesions, in HIV-seropositive women. In our study, both HIV seropositivity and higher levels of immunosuppression were important determinants of persistent HPV infection. HIV-seropositive women were about seven times as likely to have persistent infection as HIV-seronegative women, and women with CD4+ counts of less than 200 per cubic millimeter were more than twice as likely to have persistent infection as those with counts of 500 or more per cubic millimeter. The higher frequency of persistent HPV infection in HIV-seropositive women than in HIV-seronegative women may explain why squamous intraepithelial lesions occur so frequently in HIV-seropositive women.

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