MAJOR ARTICLE

Effects of Bacterial Vaginosis and Other Genital Infections on the Natural History of Human Papillomavirus Infection in HIV-1–Infected and High-Risk HIV-1–Uninfected Women

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Background. Whether the natural history of human papillomavirus (HPV) infection is affected by bacterial vaginosis (BV) or *Trichomonas vaginalis* (TV) infection has not been adequately investigated in prospective studies.

Methods. Human immunodeficiency virus 1 (HIV-1)–infected ($n = 1763$) and high-risk HIV-1–uninfected ($n = 493$) women were assessed semiannually for BV (by Nugent's criteria), TV infection (by wet mount), type-specific HPV (by polymerase chain reaction with MY09/MY11/HMB01 HPV primers), and squamous intraepithelial lesions (SIL) (by cytological examination). Sexual history was obtained from patient report at each visit. Risk factors for prevalent and incident HPV infection and SIL were evaluated by use of multivariate models.

Results. BV was associated with both prevalent and incident HPV infection but not with duration of HPV infection or incidence of SIL. TV infection was associated with incident HPV infection and with decreased duration and lower prevalence of HPV infection. TV infection had no association with development of SIL. Effects of BV and TV infection were similar in HIV-1–infected and high-risk HIV-1–uninfected women. HIV-1 infection and low $CD4^+$ lymphocyte count were strongly associated with HPV infection and development of SIL.

Conclusions. BV and TV infection may increase the risk of acquisition (or reactivation) of HPV infection, as is consistent with hypotheses that the local cervicovaginal milieu plays a role in susceptibility to HPV infection. The finding that BV did not affect persistence of HPV infection and that TV infection may shorten the duration of HPV infection helps explain the lack of effect that BV and TV infection have on development of SIL.

Human papillomavirus (HPV), a sexually transmitted DNA virus, is the central etiological agent in the development of cervical cancer [1]. Several other genital diseases, including bacterial vaginosis (BV), *Trichomonas vaginalis* (TV) infection, *Chlamydia trachomatis* (CT) infection, and genital herpes (caused by infection with herpes simplex virus [HSV]), have been implicated as risk factors for the acquisition of HPV infection or the development of cervical neoplasia. Most studies of BV have shown an association between BV and infection with HPV but have yielded conflicting results regarding the association between BV and cervical dysplasia, and each study has had limitations [2–15], most often cross-sectional design or lack of adjustment for shared risk factors. Similarly, although several large pro-

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spective studies have suggested that presence of TV on baseline cytological assessment is associated with an increased risk for the development of cervical dysplasia or cancer, these studies did not include testing for HPV and were generally unable to control for sexual risk factors [16–18]. Recent studies from several countries have found a several-fold increased risk for the development of invasive cervical cancer in women with either current/previous CT infection [19–21] or HSV2 antibodies [22]. However, in a study of women referred for colposcopy, neither CT infection nor HSV2 seropositivity was associated with severity of dysplasia [23].

BV, an alteration of the vaginal flora involving a decrease in lactobacilli and a predominance of anaerobic bacteria, is of particular interest as a possible risk factor for the acquisition of HPV infection, because it has been associated in prospective studies with an increased risk of the acquisition of other sexually transmitted infections (STIs), including those caused by HIV, CT, *Neisseria gonorrhoeae,* and HSV [24–26]. Loss of H_2O_2-producing lactobacilli or other changes in the vaginal milieu could facilitate the survival of these sexually transmitted agents in the vagina, leading to an increased rate of infection. However, in the only prospective study to date of BV and the acquisition of HPV infection, BV was found to occur simultaneously with or after HPV infection, rather than antedating the acquisition of HPV infection [15]. Thus, although BV may enhance the acquisition of some genital infections, its relationship to HPV infection remains to be clarified.

HPV infection and cervical dysplasia are more common in HIV-1–infected women than in other women [27–31]. Concomitant genital infections are common in HIV-1–infected women, and their effects on the natural history of HPV infection have not been well studied. BV was present in 42% of HIV-1–infected women at the time of enrollment into the Women's Interagency HIV Study (WIHS) [32], and BV appears to be more persistent in HIV-1–infected women [33] than in other women. Given the higher prevalence of HPV infection and frequent concomitant genital infections in HIV-1–infected women than in other women, any potential associations between HPV infection and other genital infections could be accentuated, especially in women with severe immunosuppression. Thus, we evaluated the association between current BV or TV infection at each visit and the natural history of HPV infection in a large, long-term cohort of HIV-1–infected and high-risk HIV-1–uninfected women.

SUBJECTS AND METHODS

Women were enrolled in the WIHS, a longitudinal cohort study with clinical sites in the Bronx/Manhattan, Brooklyn, Chicago, Washington DC, Los Angeles, and San Francisco. The methodology of the study and the characteristics of the cohort have been described elsewhere [34]. Briefly, after approval by the local institutional review board, 2059 HIV-1–infected women and 569 high-risk HIV-1–uninfected women were enrolled during October 1994–November 1995. Informed consent was obtained from all subjects, and all human experimentation guidelines of the US Department of Health and Human Services were followed in the conduct of the clinical research.

Women underwent detailed interviews, physical examinations, and extensive laboratory testing at baseline and every 6 months thereafter. After a general physical examination, women underwent vaginal examination by use of a speculum. Swabs of vaginal fluid were obtained for the preparation of Gram-stained smears and were placed into saline for microscopic detection of motile trichomonads. Exfoliated cervical cells for use in HPV DNA testing were obtained by cervical vaginal lavage (CVL) with 10 mL of sterile normal saline. The CVL specimens were stored on ice and processed within 6 h of collection. After the CVL, at visits 1–3, Dacron swabs were used to collect cells from the cervix for use in the detection of CT; at each visit, cells for use in Pap smears were obtained with a wooden Ayre's spatula and a cytological brush.

Blood was drawn for use in $CD4^+$ lymphocyte enumeration, by standard flow-cytometric methods, conducted in laboratories participating in the National Institute of Allergy and Infectious Diseases (NIAID) Flow Cytometry Quality Assessment Program [35], and quantitation of levels of HIV-1 RNA was conducted in laboratories participating in the NIAID Virology Quality Assurance Laboratory proficiency testing program by use of the isothermal nucleic acid sequence–based amplification method, with a lower limit of detection of 4000 copies/mL (Organon Teknika) [36]. For women in the high-risk HIV-1–uninfected cohort, HIV-1 serological status was checked at each visit.

Vaginal smears were Gram stained and were categorized, according to Nugent's criteria for evaluation of the presence of lactobacilli and other morphotypes, as either normal (score, 0–3), intermediate (score, 4–6), or BV (score, 7–10) [37], by technicians masked to the study participants' HIV-1 and HPV status. CT was detected by use of PACE-2 DNA probes (Gen-probe). Cervical cytological specimens were evaluated centrally at Dianon Systems (New York, NY) and were classified according to the 1994 Bethesda system [38]. All smears were read by 2 cytotechnologists unaware of the participants' HIV-1 status and other laboratory results, and all abnormal smears and 10% of the smears with negative results were interpreted by a cytopathologist.

CVL specimens were stored at −70°C until tested. HPV DNA was detected by use of L1 consensus primer MY09/MY11/HMB01 in polymerase chain reaction (PCR) assays, and a β-globin primer was included in each assay, to assess the adequacy of the specimens [27]. After 40 amplification cycles, the amplified material was detected by use of filters individually hybridized with biotinylated type-specific oligonucleotide probes

for multiple HPV types, including HPV 6, 11, 13, 16, 18, 26, 31, 32, 33, 34, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71 (AE8), 72, 73 (PAP238A), 81 (AE7), 82 (W13B and AE2), 83 (PAP291), 84 (PAP155), 85 (AE5), 89 (AE6), AE9, and AE10 [27]. High-risk types, determined by the risk for the development of cervical neoplasia, were HPV 16, 18, 31, and 45; intermediate-risk types were HPV 33, 35, 39, 51, 52, 56, 58, 59, 68, and 73; and low-risk types were HPV 6, 11, 40, 42, 53, 54, 61, 72, and 81.

STATISTICAL METHODS

Demographic, behavioral, clinical, and laboratory factors potentially associated with the outcomes of interest were evaluated in univariate models. Race was defined at baseline, whereas age, sexual history, smoking, injection drug use, alcohol use, concomitant infections—including BV, TV, CT and genital HSV—and, in HIV-1–infected women, $CD4^+$ lymphocyte count, level of HIV-1 RNA, and use of antiretroviral therapy were time-dependent covariates; for the number of male sex partners, smoking, injection drug use, and alcohol use, "current" was considered to be within the preceding 6 months. The use of antiretroviral therapy at each visit was classified as either none; monotherapy; combination therapy if $\geqslant$2 agents not meeting the definition of highly active antiretroviral therapy (HAART) were being used; and HAART if the regimen included $\geqslant$2 nucleoside agents with a protease inhibitor or nonnucleoside agent, $\geqslant$1 drug from each of these 3 classes, 2 protease inhibitors with 1 nucleoside agent, or an abacavir-containing regimen of $\geqslant$3 nucleosides. Cervical cytological abnormalities included prevalent and incident squamous intraepithelial lesions (SIL), defined as either low grade or high grade. For SIL analyses but not for HPV analyses, women were omitted from further observations if ablative treatment for cervical neoplasia was reported. In previous analyses, we have shown that the omission of these women from the analysis at treatment of neoplasia does not affect the assessment of HPV incidence and duration in the WIHS [39].

Prevalent HPV infection was defined as detection of any HPV DNA at a given visit, including HPV DNA that was not specifically typed (i.e., detected by use of a general consensus HPV probe only). Results of HPV tests were available for all CVL specimens obtained during visits 1–6 and for CVL specimens obtained at baseline and during visits 7–12 from a randomly selected subcohort representative of the whole WIHS cohort, resulting in 4650 person-years of follow-up in HIV-1–infected women and 1317 person-years of follow-up in high-risk HIV-1–uninfected women. To adjust for the dependency introduced by repeated observations involving the same individual, generalized estimating equations were used to estimate robust SEs for all parameter estimates [40]. For incidence and duration models, a marginal model approach for the Cox model was used based on the Wei, Lin, and Weissfeld (WLW) method of SE adjustment [41]. Incident HPV infection was defined on a type-specific basis as detection of a new type of HPV not present at any prior visit. Therefore, women contributed information for the incidence of every HPV type under study, resulting in multiple event times. Because of the interval-censored nature of the data, the midpoint method was used to estimate the actual time of HPV infection. Duration was defined as the time from incident infection to the first negative HPV test result for that particular type. Again, multiple event times are recorded for each woman in the study, and these were adjusted for by use of the WLW approach.

To assess the impact of HIV-1 status on the effects of some of the parameters, interaction parameters were estimated in the models. If the interaction term was significant, then a model that reflected the differential effect for that particular outcome (based on HIV-1 status) was included. A lack of significance indicated that the overall parameter estimate was representative of the effect within each of the 2 subgroups (an averaged effect) individually.

Multivariate models were based on careful examination of univariate results as well as on an examination of subset analyses, which gave an indication of which parameters entered into the models consistently. The final multivariate models presented are representative of the types of predictors that are important with respect to the outcomes.

To investigate the temporal relationship between BV and HPV infection, 2 Cox models were studied. The first model was the standard model in which BV was treated as a time-dependent covariate and its effect on the hazard of incident HPV infection was examined. The second model reversed the outcome and the predictor and assessed HPV infection as a predictor of incident BV. Of interest is the strength of the association between each predictor and each outcome as a way to determine the temporal relationship between BV and HPV infection.

RESULTS

Of all those enrolled in the WIHS, 1736 HIV-1–infected women and 493 high-risk HIV-1–uninfected women had $\geqslant$1 follow-up visit that had available HPV test results and are included in the present analysis. Selected characteristics of the cohort at enrollment into the study are listed in table 1. HIV-1–infected women were somewhat older, were less likely to have a current male sex partner, and were less likely to smoke than were high-risk HIV-1–uninfected women. Current injection drug use occurred in similar proportions, but past injection drug use was more frequent in HIV-1–infected women. At enrollment, 31% of the HIV-1–infected women had a $CD4^+$ lymphocyte count <200 cells/uL, and 26% had HIV-1 RNA levels >100,000 copies/mL. Rates of detection of CT, *Neisseria gonorrhoeae,* BV,

Table 1. Enrollment characteristics of the cohort, according to HIV-1 status.

Characteristic	HIV-1–infected (n = 1736)	High-risk HIV-1–uninfected (n = 493)	P[a]
Age group			<.001
<26 years	141 (8)	87 (18)	
26–29 years	168 (10)	63 (13)	
30–35 years	494 (28)	122 (25)	
36–45 years	752 (43)	188 (38)	
>45 years	181 (10)	33 (7)	
Race			.05
African American	926 (53)	259 (52)	
Hispanic	435 (25)	144 (29)	
White	329 (19)	72 (15)	
Other	46 (3)	18 (4)	
Parity			.08
0	375 (22)	130 (26)	
1	354 (20)	108 (22)	
2	369 (21)	95 (19)	
⩾3	633 (36)	160 (32)	
No. of current male sex partners			<.001
0	569 (33)	106 (22)	
1	901 (52)	266 (54)	
>1	250 (15)	117 (24)	
Current smoking	951 (55)	307 (63)	.003
Injection drug use			
Current	171 (10)	59 (12)	.20
Ever	683 (39)	157 (32)	.003
Current alcohol use			.013
None	733 (43)	182 (38)	
Light	545 (32)	146 (30)	
Moderate	274 (16)	97 (20)	
Heavy	140 (8)	55 (11)	
Current antiretroviral therapy			
None	625 (36)		
Monotherapy	991 (57)		
Combination, not HAART	115 (7)		
HAART	5 (0.3)		
$CD4^+$ lymphocyte count			
<200 cells/μL	517 (31)		
200–500 cells/μL	712 (43)		
>500 cells/μL	446 (27)		
HIV-1 RNA level			
<4000 copies/mL	482 (28)		
4001–20,000 copies/mL	330 (19)		
20,001–100,000 copies/mL	459 (26)		
>100,000 copies/mL	445 (26%)		
Vaginal smear result by Gram stain			.25
Normal	621 (36)	163 (34)	
Intermediate	341 (20)	90 (19)	
Bacterial vaginosis	743 (44)	232 (48)	
Trichomonas vaginalis on wet mount	97/1617 (6)	38/475 (8)	.15
Chlamydia trachomatis infection	10/1725 (<1)	8/491 (2)	
History of *C. trachomatis* infection	344/1710 (20)	102 (21)	.68
History of genital herpes	420/1736 (24)	37/493 (7.5)	<.001
HPV detection			
Any type	1023/1606 (64)	138/462 (30)	<.001
By generic probe only	268 (17)	72 (15)	
1 type	346 (21)	42 (9)	
2 types	169 (11)	16 (3)	
⩾3 types	240 (15)	8 (2)	

NOTE. Data are no. (%), unless otherwise indicated. HAART, highly active antiretroviral therapy; HPV, human papillomavirus.

[a] χ^2 test.

Table 2. Assessment of factors associated with detection of prevalent human papillomavirus infection.

Characteristic	Univariate OR (95% CI)	Multivariate OR (95% CI)[a]
Age, continuous, per-year increase	1.00 (0.99–1.01)	0.99 (0.98–0.99)
Race		
White	Reference	Reference
African American	1.26 (1.08–1.46)	1.26 (1.10–1.43)
Hispanic	1.00 (0.84–1.17)	1.00 (0.87–1.15)
Other	1.16 (0.81–1.67)	1.29 (0.96–1.73)
Parity, continuous	1.01 (0.99–1.01)	
No. of current male sex partners		
0	Reference	Reference
1	1.05 (0.95–1.15)	1.12 (1.03–1.23)
>1	1.00 (0.88–1.13)	1.13 (1.01–1.26)
Current smoking	1.20 (1.09–1.33)	1.22 (1.12–1.33)
Current injection drug use	0.89 (0.74–1.06)	
Current alcohol use		
None	Reference	
Light	0.92 (0.83–1.01)	
Moderate	0.88 (0.78–0.99)	
Heavy	1.10 (0.94–1.28)	
Current antiretroviral therapy		
HIV-1 negative	Reference	
None	3.68 (3.16–4.29)	
Monotherapy	5.27 (4.54–6.10)	
Combination, not HAART	4.67 (3.98–5.48)	
HAART	4.63 (3.95–5.41)	
$CD4^+$ lymphocyte count		
HIV-1 negative	Reference	Reference
<200 cells/μL	6.59 (5.69–7.65)	6.91 (5.94–8.03)
200–500 cells/μL	4.22 (3.64–4.90)	4.35 (3.74–5.05)
>500 cells/μL	2.46 (2.07–2.92)	2.59 (2.18–3.07)
HIV-1 RNA level		
HIV-1 negative	Reference	
<4000 copies/mL	3.17 (2.72–3.70)	
4001–20,000 copies/mL	4.10 (3.50–4.80)	
20,001–100,000 copies/mL	5.44 (4.67–6.33)	
>100,000 copies/mL	6.49 (5.57–7.56)	
Vaginal smear result by Gram stain		
Normal	Reference	Reference
Intermediate	1.28 (1.17–1.40)	1.13 (1.03–1.24)
Bacterial vaginosis	1.28 (1.16–1.41)	1.17 (1.08–1.27)
Trichomonas vaginalis on wet mount	0.95 (0.80–1.12)	0.82 (0.71–0.96)
History of *Chlamydia trachomatis* infection	1.15 (0.99–1.32)	
History of genital herpes	1.18 (1.04–1.34)	

NOTE. CI, confidence interval; HAART, highly active antiretroviral therapy; OR, odds ratio.

[a] Only significant multivariate results are shown.

and TV by wet mount did not differ between the HIV-1–infected women and the high-risk HIV-1–uninfected women, but a history of genital HSV infection was more frequent in HIV-1–infected women than in high-risk HIV-1–uninfected women. Compared with high-risk HIV-1–uninfected women, HIV-1–infected women were more likely to have HPV detected and were more likely to have $\geq$1 type of HPV.

The prevalence of HPV infection at visits 1–12 was 48%–55%. Risk factors for detection of prevalent HPV infection, summarized over the first 12 visits, are shown in table 2. Because stratification by HIV-1 status did not change the results of this or subsequent analyses, data from the 2 groups were analyzed together. On multivariate analyses, factors significantly associated with prevalent HPV infection were age (decreasing risk with increasing age), African American race, >1 current male sex partner, current smoking, HIV-1 seropositivity with

Table 3. Univariate and multivariate assessment of factors associated with detection of incident human papillomavirus infection.

Characteristic	Univariate OR (95% CI)	Multivariate OR (95% CI)[a]
Age, continuous, per-year increase	0.99 (0.99–1.00)	0.99 (0.98–1.00)
Race		
White	Reference	Reference
African American	1.25 (1.15–1.35)	1.15 (0.98–1.35)
Hispanic	0.94 (0.86–1.04)	0.97 (0.81–1.16)
Other	1.08 (0.88–1.31)	1.08 (0.74–1.57)
Parity, continuous	1.02 (0.99–1.06)	
No. of current male sex partners		
0	Reference	Reference
1	1.52 (1.40–1.65)	1.31 (1.14–1.50)
>1	1.23 (1.16–1.32)	1.59 (1.35–1.88)
Current smoking	1.23 (1.16–1.31)	1.96 (1.75–2.20)
Current injection drug use	0.87 (0.78–0.97)	
Current alcohol use		
None	Reference	
Light	1.00 (0.94–1.08)	
Moderate	1.02 (0.94–1.10)	
Heavy	1.22 (1.10–1.34)	
Current antiretroviral therapy		
HIV-1 negative	Reference	
None	2.93 (2.44–3.52)	
Monotherapy	4.04 (3.37–4.85)	
Combination, not HAART	3.55 (2.28–4.39)	
HAART	3.32 (2.17–4.08)	
$CD4^+$ lymphocyte count		
HIV-1 negative	Reference	Reference
<200 cells/μL	4.70 (3.92–5.64)	5.19 (4.30–6.26)
200–500 cells/μL	3.34 (2.79–3.97)	3.61 (3.01–4.32)
>500 cells/μL	2.10 (1.71–2.55)	2.12 (1.73–2.60)
HIV-1 RNA level		
HIV-1 negative	Reference	
<4000 copies/mL	1.85 (1.57–2.18)	
4001–20,000 copies/mL	2.37 (1.98–2.84)	
20,001–100,000 copies/mL	3.36 (2.84–3.97)	
>100,000 copies/mL	3.79 (3.18–4.52)	
Vaginal smear result by Gram stain		
Normal	Reference	Reference
Intermediate	1.37 (1.28–1.47)	1.23 (1.07–1.41)
Bacterial vaginosis	1.58 (1.49–1.68)	1.41 (1.25–1.59)
Trichomonas vaginalis on wet mount	1.63 (1.49–1.78)	1.36 (1.14–1.62)
History of *Chlamydia trachomatis* infection	0.94 (0.84–1.05)	
History of genital herpes	1.10 (0.96–1.27)	

NOTE. CI, confidence interval; HAART, highly active antiretroviral therapy; OR, odds ratio.

[a] Only significant multivariate results are shown.

a decreasing $CD4^+$ lymphocyte count, intermediate score or BV by Gram stain, and TV on wet mount (decreased risk). In examining the impact of HIV-1 infection on HPV and SIL outcomes, we found that the $CD4^+$ lymphocyte count was the best predictor. The addition of HIV-1 RNA level or antiretroviral therapy group to models that included $CD4^+$ lymphocyte count did not change the findings significantly, so these variables were not included in the final models. History of CT or genital HSV infection was not associated with detection of prevalent HPV infection in multivariate analyses.

The rate of detection of $\geq$1 new type of HPV at follow-up visits was 36%–50%. Factors associated with detection of a new HPV type (incident HPV) are shown in table 3. On multivariate analyses, $\geq$1 male sex partner, current smoking, HIV-1 seropositivity with a decreasing $CD4^+$ lymphocyte count, intermediate score or BV by Gram stain, and TV infection remained

significantly associated with detection of incident HPV. Specifically, intermediate score by Gram stain (hazard ratio [HR], 1.23 [95% confidence interval (CI), 1.07–1.41]), BV (HR, 1.41 [95% CI, 1.25–1.9]), and TV (HR, 1.36 [95% CI, 1.14–1.62]) were associated with incident HPV infection in multivariate models, but history of CT and genital HSV infection were not.

Examination of the temporal relationship between BV and HPV infection showed no discernible pattern. In women with both incident BV and HPV, the numbers of women who had both infections at the same time, who had BV at the visit prior to the visit at which HPV infection was detected, and who had HPV infection at the visit prior to the visit at which BV was detected were roughly equal. BV was associated with an increased risk of detection of HPV, and HPV infection was associated with an increased risk of BV.

In women with incident HPV infection, factors associated with the duration of infection were assessed. An HR >1 indicated a greater likelihood of infection persisting at the next visit, whereas an HR <1 indicated a higher probability of resolution. Factors associated with the duration of infection in multivariate analyses are shown in table 4 and included Hispanic ethnicity (shorter duration), $CD4^+$ lymphocyte count (longer duration with lower counts), current injection drug use (longer duration), and TV on wet mount (shorter duration). BV, history of CT, and history of genital HSV infection were not associated with the persistence of HPV infection.

Given the association of BV and TV with prevalent and incident HPV infection, we assessed the effects of these coinfections on the prevalence and incidence of cervical cytological abnormalities. The prevalence of SIL at each visit was 6%–14%. Factors associated with prevalent SIL on univariate analyses included age (decreasing risk with increasing age), race (increased for all races/ethnicities other than white), current injection drug use (decreased risk), $CD4^+$ lymphocyte count (increasing risk with decreasing cell count), HIV-1 RNA level, and number of HPV types detected. On multivariate analyses, only African American race (odds ratio [OR], 1.31 [95% CI, 1.00–1.73]) or Hispanic ethnicity (OR, 1.46 [95% CI, 1.08–1.97]), $CD4^+$ lymphocyte count (OR, 1.95 [95% CI, 1.33–2.86], for $CD4^+$ count >500 cells/μL; OR, 3.15 [95% CI, 2.21–4.50], for $CD4^+$ count 200–500 cells/μL; OR, 4.93 [95% CI, 3.41–7.13], for $CD4^+$ count <200 cells/μL, all compared with levels in high-risk HIV-1–uninfected women), detection of HPV (OR, 2.24 [95% CI, 1.80–2.77], for 1 type detected; OR, 3.83 [95% CI, 2.34–6.27], for ⩾3 types detected, compared with no HPV detection), and category of HPV type detected (OR, 1.39 [95% CI, 1.12–1.73], for low-risk types; OR, 1.52 [95% CI, 1.20–1.93], for high-risk types) were significantly associated with prevalent SIL.

The rate of incident SIL was 0%–4% over visits 2–12. Factors associated with incident SIL on univariate analyses included age (decreasing risk with increasing age), ⩾1 male sex partner, current injection drug use (decreased risk), $CD4^+$ lymphocyte count (increasing risk with decreasing level), HIV-1 RNA level, and number of HPV types detected. BV, TV, history of CT, and genital HSV infection were not associated with incident SIL on univariate analyses. In the final multivariate model, factors associated with incident SIL were age (HR, 0.95/year [95% CI, 0.93–0.97]), $CD4^+$ lymphocyte count <500 cells/μL (HR, 2.21 [95% CI, 1.27–3.50], for $CD4^+$ count 200–500 cells/μL; HR, 2.78 [95% CI, 1.60–4.82], for $CD4^+$ count <200 cells/μL), detection of HPV (HR, 2.01 [95% CI, 1.39–2.90], for 1 type detected; HR, 5.73 [95% CI, 2.99–10.98], for ⩾3 types detected), and category of HPV type detected (HR, 4.12 [95% CI, 2.38–7.12], for low-risk types; HR, 4.66 [95% CI, 2.74–7.87], for high-risk types).

DISCUSSION

Our study is unique in its evaluation of the effects that concomitant vaginal infections have over time on the prevalence and incidence of HPV infections and of SIL in HIV-1–infected and high-risk HIV-1–uninfected women. BV was associated with an increased risk of prevalent and incident HPV infection but not with the duration of HPV infection or development of SIL. The association between BV and HPV persisted even after adjustment for number of lifetime and number of current male sex partners, which suggests that the association is not simply the result of shared risk factors for acquisition. These data are consistent with the results of 4 previous studies—3 cross-sectional and 1 prospective—that found an increased rate of HPV infection in women with BV [2, 3, 6], including HIV-1–infected women in the HIV Epidemiologic Research Study [4]. A cross-sectional study of women in Costa Rica did not find an increased rate of BV in women with HPV, compared with women without HPV [8]. A small prospective study of adolescents did not find a history of BV, diagnosed by nonstandard criteria, to be a risk factor for incident HPV infection [5]. Interestingly, a study of college students who had a limited number of sex partners found that HPV infection most often preceded BV [15]. We did not find such a time-dependent relationship but instead found HPV infection or BV was associated with an increased detection of the other condition. HPV infection may favor changes in the vaginal milieu that facilitate development of BV, and women with BV may be more susceptible to the acquisition or reactivation of HPV infection because of their increased production of sialidase and resultant changes in the cervical mucous barrier, decreased production of H_2O_2, changes in production of cytokines, or other factors [42–45]. Notably, detection of incident HPV infection in our cohort may represent either initial acquisition or reactivation of latent infection. Although this is true in all prospective studies of HPV, it is a particularly important consideration in our

Table 4. Factors associated with persistence of human papillomavirus infection.

Characteristic	Univariate OR (95% CI)	Multivariate OR (95% CI)[a]
Age, continuous, per-year increase	1.00 (1.00–1.01)	
Race		
White	Reference	Reference
African American	0.93 (0.87–1.00)	0.91 (0.79–1.04)
Hispanic	0.83 (0.77–0.91)	0.82 (0.69–0.96)
Other	0.83 (0.69–1.00)	0.81 (0.58–1.14)
Parity, continuous	0.99 (0.96–1.02)	
No. of current male sex partners		
0	Reference	
1	0.96 (0.85–1.08)	
>1	0.92 (0.79–1.06)	
Current smoking	1.00 (0.92–1.05)	
Current injection drug use	0.87 (0.77–0.97)	
Current alcohol use		
None	Reference	
Light	1.01 (0.89–1.14)	
Moderate	0.96 (0.84–1.11)	
Heavy	0.92 (0.76–1.11)	
Current antiretroviral therapy		
None	1.27 (1.06–1.49)	
Monotherapy	1.25 (1.04–1.51)	
Combination, not HAART	1.25 (1.03–1.51)	
HAART	1.28 (1.06–1.54)	
$CD4^+$ lymphocyte count		
HIV-1 negative	Reference	Reference
<200 cells/μL	1.07 (0.89–1.30)	1.45 (1.20–1.75)
200–500 cells/μL	1.20 (1.01–1.43)	1.20 (1.02–1.43)
>500 cells/μL	1.47 (1.22–1.75)	1.06 (0.88–1.28)
HIV-1 RNA level		
HIV-1 negative	Reference	
<4000 copies/mL	1.20 (1.02–1.45)	
4001–20,000 copies/mL	1.19 (0.98–1.43)	
20,001–100,000 copies/mL	1.41 (1.18–1.69)	
>100,000 copies/mL	1.32 (1.08–1.61)	
Vaginal smear result by Gram stain		
Normal	Reference	
Intermediate	1.02 (0.94–1.09)	
Bacterial vaginosis	1.03 (0.97–1.09)	
Trichomonas vaginalis on wet mount	0.76 (0.67–0.85)	0.76 (0.60–0.96)
History of *Chlamydia trachomatis* infection	1.32 (0.93–1.85)	
History of genital herpes	0.99 (0.80–1.23)	

NOTE. An odds ratio (OR) >1 indicates a higher likelihood of persistence, whereas OR < 1 indicates a greater probability of resolution. CI, confidence interval; HAART, highly active antiretroviral therapy.

[a] Only significant multivariate results are shown.

study because of the older age, higher number of lifetime male sex partners, and changes in immune function in our cohort. Whether the effect of BV on the detection of incident HPV infection is caused by an effect on susceptibility for acquiring a new HPV infection or by reactivation is, therefore, not resolved by our analysis.

Our study is also unique in its evaluation of the effects that genital infections have on the duration of HPV infection in HIV-1–infected and high-risk HIV-1–uninfected women. The failure to detect an effect of BV on the duration of HPV infection is consistent with the observed lack of association between BV and the development of SIL, because persistent HPV infection appears to be required for the development of cervical neoplasia [5, 46]. The results of previous, primarily cross-sectional, studies on the impact that BV has on cervical dysplasia have been conflicting [5, 7–12, 14, 47]. Studies that included

only HPV-positive women did not show an association between BV and dysplasia, as is consistent with our findings.

TV infection was associated with an increased incidence but a decreased prevalence of HPV infection, as is consistent with the finding of decreased duration of HPV infection with concomitant TV infection. TV infection had no effect on the prevalence or incidence of SIL, which reflects the complex relationship between TV infection and the natural history of HPV infection. Previous studies of the impact that TV infection has on cervical disease have focused on the development of cervical intraepithelial neoplasia or invasive cancer rather than on HPV infection and have evaluated TV infection as diagnosed by cervical cytological examination, which is not as sensitive or as specific as wet mount. Results of 3 large studies of >75,000 women comparing baseline results of cytological examination with information in long-term cancer or dysplasia registries but did not include HPV testing suggested that TV infection confers an increased risk for the development of cervical neoplasia over time [16–18], but only 1 study adjusted for risk factors associated with sexual activity that may account for the increased acquisition of both TV infection and HPV infection [17]. Two studies that assessed levels of antibodies to TV in women with cervical cancer compared with those in control subjects found an increased seroprevalence of TV in women with cervical cancer, compared with that in control subjects, but there was no adjustment for other risk factors [48, 49]. We did not find an increased risk for the development of SIL in our cohort, as is consistent with the decreased duration of HPV infection, which, in turn, may be related to the marked inflammatory response often directed at TV.

Past or current CT by patient report and limited testing during the present study was not associated with HPV infection or the development of SIL in our cohort, despite a history of CT in >20% of subjects at baseline. Two major studies of serological evidence of CT detected a relative risk (RR) of 1.5–2.1 for development of cervical cancer in women who had antibodies to CT, compared with women who did not have antibodies to CT [19, 20]. In a multicountry study that evaluated CT infection by PCR conducted on Pap smears and cervical biopsy specimens, the RR for the development of cervical cancer in women who had ever tested positive for CT was 17.1, compared with women who had never tested positive [21]. In 2 studies, CT positivity was independent of HPV positivity [19, 21]. Conversely, in a study on women with dysplasia, detection of CT by PCR or by serological assessment in 2 different assays was not associated with the grade of dysplasia [23]; the results of the present study are consistent with these results. However, the 3 other studies used high-grade lesions or cervical cancer as the end point, which suggests that, in the longer term, history of CT infection may play a role in cervical carcinogenesis or that past CT infection may be a marker of a higher likelihood of exposure to oncogenic HPV types.

A history of genital HSV infection was not associated with HPV positivity or the development of SIL, but we did not evaluate the presence of HSV infection by use of serological assessment or PCR. In vitro data suggests that the HSV2 genome may induce a malignant transformation of HPV-immortalized cervical cells [50], but clinical studies that incorporated a history of HSV infection or used less-specific HSV type-specific antibody assays have yielded conflicting results (reviewed in [19]). A study of type-specific HSV1 and HSV2 antibody assays found that HSV2 antibody positivity was roughly twice as common in women who had cervical cancer than in control women [22]. In HPV-positive women, HSV2 seropositivity was associated with squamous-cell carcinoma (adjusted OR [AOR], 2.19 [95% CI, 1.41–3.40]) and adenocarcinoma or adenosquamous-cell carcinoma (AOR, 3.37 [95% CI, 1.47–7.74]) [22]. However, as with CT infection, HSV2 antibody positivity was not associated with a higher grade of dysplasia in a cohort of women referred for colposcopy [23]. HSV2 infection may be a cofactor for progression to cervical cancer that involves late stages of tumorigenesis or, as discussed above, antibodies to HSV or the presence of another STI could act as a surrogate marker of exposure to oncogenic HPV.

The factors most strongly associated with detection and duration of HPV infection in the present study were HIV-1 seropositivity and decreased $CD4^+$ lymphocyte count, as is consistent with the results of previous studies of HIV-1–infected and high-risk HIV-1–uninfected women [4, 27, 28, 51]. Current smoking, as has been noted elsewhere [52], and number of male sex partners were also risk factors for prevalent and incident HPV infection in our cohort but were not risk factors for the duration of HPV infection. Of the many factors that we evaluated, only $CD4^+$ lymphocyte count and number and types of HPV detected were predictive for the development of SIL. These risk factors for development of SIL have been well documented [31, 53, 54].

Limitations of the present study include the detection of TV by a relatively insensitive wet mount and the lack of serological testing for CT and HSV. It is possible that the interaction between TV and HPV in women who have higher levels of pathogens and inflammatory responses, as detected by wet mount, is different than that in women who have lower levels of pathogens that can be detected only by culture or nucleic-acid amplification tests. In addition, the relationship between TV and HPV may be different in younger women, who are more likely to have multiple concomitant genital infections, than in older women. Future testing of archived specimens may further clarify the interaction between cervical dysplasia and CT infection and HSV seropositivity, after accounting for concurrent reproductive tract infections. More frequent follow-up visits by our cohort may

have allowed for better clarification of the temporal relationship between BV and the detection of incident HPV infection.

Our results suggest that BV and TV infection do not have a major impact on the development of cervical neoplasia in HIV-1–infected and high-risk HIV-1–uninfected women. However, our findings provide prospective evidence that variations in the cervicovaginal milieu resulting from coinfections may have significant effects on HPV infection and its natural history. These findings underscore the need for further research to better understand the physiology of the female genital tract and the local response to pathogens.

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