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Determinants of Newly Detected Human Papillomavirus Infection in HIV-Infected and HIV-Uninfected Injection Drug Using Women

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Abstract

Background—We sought to identify factors associated with newly detected human papillomavirus (HPV) infection in a high-risk cohort of injection drug using women in Baltimore, MD.

Methods—We studied 146 HIV-infected and 73 HIV-uninfected female participants in a 5-year prospective HIV natural history study. We examined the association of sexual and nonsexual risk factors and newly detected type-specific HPV infection as determined by consensus PCR between consecutive visits.

Results—Newly detected HPV was more common among HIV-infected versus HIV-uninfected women (30% and 6%, respectively; P <0.01). Among the entire cohort, recent crack use (OR, 1.7; 95% CI, 1.1−2.6) and HIV infection/CD4 cell count were independent predictors for new HPV detection (HIV-uninfected as reference, OR, 4.6; 95% CI, 2.3−8.9, OR, 5.4; 95% CI, 2.8−10.3, and OR, 10.9; 95% CI, 5.5−21.7 for HIV-infected CD4 >500, 200−500, and <200, respectively). Among HIV-uninfected women, recent marijuana use was an independent predictor of newly detected HPV infection (OR, 3.5; 95% CI, 1.3−9.5).

Conclusions—Newly detected HPV clearly increased with greater immunosuppression in HIV-infected injection drug users. Larger studies of HIV-uninfected and infected high-risk individuals are needed to clarify the independent associations of crack and marijuana use with new (or reactivated) HPV infection.

Epidemiologic studies have confirmed that high-risk human papillomavirus (HPV) infection is the central cause of invasive cervical cancer. HPV is an extremely common sexually transmitted infection worldwide. One recent study estimated the overall HPV prevalence to be 26.8% among females aged 14 to 59 years in the United States.1 The total direct medical costs of HPV in the United States, $2.9 billion annually, are comparable to those for human

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immunodeficiency virus (HIV), $3.0 billion annually, among individuals aged 15 to 24 years.2 Risk factors for HPV infection include increased number of sexual partners, immune suppression, smoking, and possibly hormonal contraceptives use.3,4

Injection drug users, especially women, have high rates of sexually transmitted infections, such as herpes simplex 2 and syphilis.5 In a recent study among injection drug using women, the primary predictor of incident HPV infection was HIV infection.6 HPV prevalence and incidence is 2- to 4-times higher among women with HIV infection.7 Few other determinants of newly detected HPV in this population have been reported and these may vary by HIV serostatus. The objective of this analysis was to explore the potential determinants of newly detected HPV infection among HIV-infected and HIV-uninfected injection drug using women enrolled in a prospective cohort study conducted in Baltimore, MD.

MATERIALS AND METHODS

Study Design

The rationale, design, and methods of the parent study, AIDS Link to Intravenous Experiences (ALIVE), have been described elsewhere. In brief, between February 1988 and March 1989, 2921 individuals from Baltimore, MD, were recruited to study the natural history of HIV infection among injection drug users.8,9 After providing informed consent, participants underwent interviewer-administered questionnaires and blood specimen collection.9 HIV serostatus was determined using an enzyme-linked immunosorbent assay (Genetic Systems, Redmond, WA) and confirmed using Western blot (DuPont, Wilmington, DE).10 All HIV-infected and a selection of the HIV-uninfected individuals who returned for test results were invited to the clinical and immunologic component of the ALIVE study, consisting of semiannual follow-up visits to assess health, drug use, sexual behaviors, physical examination, and HIV/CD4 change during the previous 6 months. The Institutional Review Board of the Johns Hopkins School of Hygiene and Public Health in Baltimore, MD reviewed and approved all study procedures.9

From September 1992 to September 1997, 268 women in the ALIVE study consented to participate in a prospective gynecological substudy.11 This involved a gynecological exam at each visit, during which cervical smears and cervicovaginal lavage (CVL) specimens were collected.11,12

Laboratory Methods

CVL specimens underwent PCR amplification of HPV genomic sequences using MY09/MY11/HMB01 L1 consensus primers.12 Negative controls monitored for specimen contamination and β-globin controls were included to ensure valid HPV test results. CVL specimens were tested for 26 specific HPV types (6,11,16,18,26,31,33,35,39,40,45,51,52,52,53,54,55,56,58,59,66, 68,73,82,83,84) using oligonucleotide dot blot hybridization methods. CD4 cell counts were determined by 3-color flow cytometry in combination with complete blood count and differential.10

Statistical Analysis

A total of 268 women fulfilled the eligibility criteria for the gynecologic substudy, which included participating in the clinical and immunologic component of ALIVE and being HIV-infected or part of a HIV-uninfected convenience sample. For the present analysis, we excluded observations (i.e., visits) with missing or incomplete sexual exposure data and observations with greater than 7 months between the index visit (*t*) and the immediately preceding visit (*t-1*). This latter exclusion was implemented to minimize misclassification of

the outcome and time-varying covariates, which were collected at each study visit relative to the previous 6 months. The remaining study population consisted of 146 HIV-infected and 73 HIV-uninfected injection drug using women who contributed 775 observations to the final analytic dataset. The unit of analysis was study visit.

Fixed (time independent) variables obtained from the ALIVE enrollment questionnaire included race, age, lifetime use of oral contraceptives, number of live births in lifetime (i.e., parity), number of times pregnant, current pregnancy, and number of different male sex partners in the last 10 years (total lifetime partners was not assessed in this study).

Time-varying exposures, collected during follow-up visits and at ALIVE enrollment, reflected the previous 6 months: smoking, smoking frequency, crack use, alcohol use, injection of heroin only, injection of cocaine only, injection of both heroin and cocaine (not at the same time), snorted cocaine, snorted heroin, smoked heroin, injection of “speedball” (heroin and cocaine at the same time), marijuana, street methadone, number of male sex partners, any high-risk sex, any sexually transmitted disease, date of last menstrual period, HIV serostatus, antiretroviral therapy, including information on class of therapy (e.g., protease inhibitors), CD4 cell count per mm^3, type-specific HPV testing, β-globin HPV control, and Pap test result. High-risk sex was defined as anonymous and/or traded sex, sex with multiple partners without always using condom, and/or sex with injection drug user(s) without always using condom. Data specific to use of methamphetamines, morphine, or other illicit drugs were not collected in a standardized method during this study time period within the parent study, ALIVE.

The outcome was defined as 1 or more type-specific HPV infection(s) at an index follow-up visit (*t*) not detected at the immediately preceding visit (*t-1*) with less than 7 months between the 2 consecutive visits. Given this outcome definition, observations excluded from the analyses were significantly more likely to be from women with lower CD4 cell counts, as compared to observations included in the analyses ($P = 0.01$). Because detection of new HPV types at each visit was independent of previous HPV infections with other types, a participant could contribute multiple outcomes during the longitudinal study period.

We calculated the proportion of observations with the outcome in categories defined by the covariates and tested for differences using Pearson's χ^2. We modeled ordinal categorical variables as continuous variables to test for linear trends. Results were considered statistically significant if $P \leq 0.05$.

To examine the relationship between newly detected type-specific HPV infection and the covariates, multivariate logistic regression models were constructed among the entire cohort and in HIV strata. Generalized estimating equations (GEE) methods with a logit link, exchangeable working correlation structure, and robust standard error estimation were used to take subject-specific correlation of repeated measurements into account.13 To establish face validity of all our multivariate models, we included 2 *a priori* risk factors for HPV infection: sexual activity and younger age. We used bivariate screening to evaluate the associations between the outcome and each of the covariates.14 Covariates that demonstrated statistically significant bivariate associations or borderline statistically significant bivariate associations with new HPV detection were added to the multivariate models. (These models by default included age category and the sexual activity variable that demonstrated the strongest association in bivariate screening.) We then evaluated the remaining covariates to assess the impact of adjustment (by age, sexual activity, and those covariates identified in bivariate screening) upon their crude associations with the outcome. Variables that demonstrated statistically significant adjusted associations with new HPV detection were then added to the final multivariate models.

To explore the effect of crack use on HPV infection, we examined the association between recent crack use and abnormal Pap findings using the methods described above.

We also conducted sensitivity analyses. To understand the potential effect of intervening false negative HPV results on defining the outcome, we analyzed the type-specific HPV test results of the visit immediately preceding the "visit-pair" used to define the outcome. The visit-pair approach compared HPV results between visit *t* and visit *t-1*. This sensitivity analysis examined the HPV results of visit *t-2* in relation the visit-pair. We quantified the number of outcomes that were preceded by a negative type-specific HPV result [i.e., for each HPV type, a pattern of no infection (0) at *t-2*, no infection (0) at *t-1*, and infection (1) at t^i]. We then quantified the outcomes that were preceded by a positive type-specific result [i.e., for each HPV type, a pattern of infection (1) at *t-2*, no infection (0) at *t-1*, and infection (1) at t^i].

To take a more conservative approach at defining the outcome and a sexual exposure variable, we calculated the number of visits with 1 or more type-specific HPV infection(s) not detected at the 2 immediately preceding visits with less than 7 months between consecutive visits and with 1 or more male sex partners reported in both or neither of the 2 immediately preceding intervals. As this approach required 3 visits with less than 7 months between consecutive visits, our sample size was substantially reduced, such that only 379 observations among 139 women were included in the sensitivity analysis.

All analyses were performed using Stata/SE version 10.1 (StataCorp, College Station, TX).

RESULTS

Study Population

At enrollment in the gynecological substudy, the cohort of 146 HIV-infected (67%) and 73 HIV-uninfected (33%) women had a mean age of 37 years (standard deviation 6.6) and was 95% black. The number of visits per participant ranged from 2 to 10 (mean 4.5). HIV-infected women were more likely to report a greater number of male sex partners in the last 10 years as compared to HIV-uninfected women ($P = 0.01$). There were no significant differences by HIV status in race, age, recent use of various drugs, recent sexual risk behaviors, ever oral contraceptive use, and number of live births in lifetime (Table 1). Among HIV-infected women at enrollment, only 1 had received highly active antiretroviral therapy (HAART), defined as a combination of at least 3 antiretroviral drugs (protease inhibitors, nucleoside reverse transcriptase inhibitors, and/or nonnucleoside reverse transcriptase inhibitors), and 43% had received mono- or dual-antiretroviral therapy. During study follow-up through 1997, 13 HIV-infected women (9%) started HAART.

Newly Detected HPV Infection

New type-specific HPV infection was detected in 22% of visits overall. Newly detected HPV was more common among visits of HIV-infected versus uninfected women (30% and 6%, respectively; $P < 0.01$) and among visits of younger women (29%, 24%, 17%, 15% for ages <35, 35−39, 40−45, >45 years, respectively; $P < 0.01$). New HPV detection was similarly frequent among visits of women reporting 1 or more male sex partners in the last 6 months and among those reporting no male sex partners in the last 6 months (22% and 21%, respectively; $P = 0.7$). New HPV detection was more common among visits of women who, at enrollment, reported a greater number of male sex partners in the last 10 years (13%, 21%, 26% for 0−2, 3−7, >7 partners, respectively; $P < 0.01$).

For visits among HIV-infected women, newly detected HPV was more common among those with lower CD4 cell counts (23%, 28%, 40% for CD4 >500, 200−500, and <200

respectively; P <0.01). Recent sexual activity, however, did not vary by CD4 cell count; 54%, 53%, 50% of HIV-infected women reported 1 or more male sex partners in the last 6 months for CD4 cell count <500, 200 to 500, and <200, respectively; P = 0.7).

Among visits from HIV-uninfected women, for several drug behaviors, newly detected HPV was more often observed among recent users as compared to nonusers. These included crack (P = 0.06), alcohol (P = 0.05), marijuana (P <0.01), injection of cocaine (P = 0.02), injection of speedball (P = 0.09), and snorted heroin (P = 0.02). Among visits from HIV-infected women, such associations were not observed, except for recent crack use (P = 0.02) (data not shown). The specificities of these findings were further examined with adjustment for sexual behaviors in multivariate modeling. The prevalence of use of snorted cocaine, smoked heroin, and street methadone was less than 10%, such that we lacked overall power to analyze these data.

For visits among all women, regardless of HIV serostatus, newly detected HPV infection did not differ by number of live births in lifetime (P = 0.22), current pregnancy at enrollment (P = 0.18), number of times pregnant at enrollment (P = 0.62), or by women reporting their most recent menstrual period within 12 months (vs. those reporting their most recent period in greater than 12 months) (P = 0.22) (data not shown).

Determinants of Newly Detected HPV Infection

In bivariate analyses, younger age category, decreasing CD4 count among visits from HIV-infected women, and greater number of male sex partners in the last 10 years (assessed at enrollment) were positively associated with newly detected HPV (Table 2). In multivariate analyses, recent crack use (OR, 1.7; 95% CI, 1.1−2.6), and HIV/CD4 category (HIV-uninfected as reference, OR, 4.6; 95% CI, 2.3−8.9; OR; 5.4; 95% CI; 2.8−10.3; and OR, 10.9; 95% CI, 5.5−21.7 for HIV-infected CD4 >500, 200−500, and <200, respectively) remained independent predictors of newly detected HPV infection (Table 2). The independent association of recent crack use and HIV/CD4 category did not change when adjusting for other correlates of sexual behavior, including any high-risk sex in the last 6 months and number of male sex partners in the last 6 months. Neither of these markers of sexual risk was associated at a statistically significant level with new HPV detection in multivariate analyses (data not shown).

Because of the strong effect of HIV infection/CD4 cell count category, we examined determinants of the outcome stratified by HIV serostatus. Although the numbers were limited for visits among HIV-uninfected women, 3 covariates were significantly associated with new HPV detection in bivariate analyses: use of marijuana, injection of cocaine only, and injection of both heroin and cocaine, all within the last 6 months (Table 3). In the final multivariate model including age, number of male sex partners in last 6 months, recent use of marijuana, recent injection of cocaine only, and recent injection of both heroin and cocaine, we observed marijuana to be an independent predictor of new HPV detection (OR, 3.5; 95% CI, 1.3−9.5) (Table 3). The associations of drug behaviors with new HPV detection did not change when adjusting for any correlates of sexual behavior during multivariate modeling (data not shown).

For visits among HIV-infected women, bivariate analyses revealed that decreasing CD4 cell count category, crack use in the last 6 months, any antiretroviral therapy in the last 6 months, and 2 sexual behavior variables (e.g., number of male sex partners in the last 6 months, number of male sex partners in the last 10 years, assessed at enrollment) were associated with newly detected HPV (Table 3). Multivariate analyses produced 2 independent predictors of new HPV detection among visits from HIV-infected women: CD4 cell count category (CD4 >500 as reference, OR, 1.2; 95% CI, 0.7−2.0 and OR, 2.0; 95%

CI, 1.1−3.6 for CD4 200−500 and <200, respectively) and number of male sex partners in last 6 months (0 as reference, OR, 1.6; 95% CI, 1.1−2.4 and OR, 0.9; 95% CI, 0.4−2.1 for 1 sex partner and >1 sex partner, respectively). In these same adjusted analyses, we observed borderline statistically significant associations with the outcome for age category, recent crack use, and recent antiretroviral therapy (Table 3).

To explore the effect of crack use on HPV infection, we examined the association between recent crack use and abnormal Pap findings. Pap results differed by recent crack use among visits of HIV-infected women ($P = 0.04$) but not among visits of those uninfected ($P = 0.70$). For visits of HIV-infected women, the unadjusted odds ratio of recent crack use for the outcome of abnormal Pap (vs. normal Pap) was 1.4; 95% CI, 0.8 to 2.5. In similar analyses stratified by CD4 category, we observed an effect of crack on abnormal Pap result among the lowest category of CD4 cell count (<200 cells per mm^3), OR, 2.4; 95% CI, 1.1 to 5.1. The crack estimates for the 2 remaining categories of CD4 cell count (200−500 and >500) were OR, 1.4; 95% CI, 0.6 to 3.2 and OR, 1.2; 95% CI, 0.4 to 3.6, respectively. When adjusting the association between crack and abnormal Pap for CD4 cell count category among visits from HIV-infected women, the adjusted odds ratio for crack remained largely unchanged (OR, 1.5; 95% CI, 0.8−2.5) (data not shown).

Sensitivity Analyses

To understand the potential effect of intervening false negative HPV results on defining the outcome, we analyzed the type-specific HPV test results of the visit immediately preceding the visit-pair used to define the outcome. This required that a participant had at least 3 consecutive visits (*t*, *t-1*, and *t-2*) with less than 7 months between *t* and *t-1*. Among the 135 outcomes that met these criteria, 79% (n = 107) were preceded by a negative type-specific HPV result [i.e., for each HPV type, a pattern of no infection (0) at *t-2*, no infection (0) at *t-1*, and infection (1) at *t*] and 30% (n = 40) were preceded by a positive type-specific result [i.e., for each HPV type, a pattern of infection (1) at *t-2*, no infection (0) at *t-1*, and infection (1) at *t*]. Among the 135 outcomes, 9% (n = 12) were observed to have both infection patterns. This is explained by the outcome definition of 1 or more newly detected type-specific HPV infection(s).

To further examine the robustness of our results and minimize potential misclassification, we redefined the outcome and a variable representing recent sexual exposure opportunity (e.g., 1 or more male sex partners in the last 6 months). We calculated the number of visits with 1 or more type-specific HPV infection(s) not detected at the 2 immediately preceding visits with less than 7 months between consecutive visits and with 1 or more male sex partners reported in both or neither of the 2 immediately preceding intervals. Only 379 observations among 139 women met these criteria.

In bivariate analyses among this subset of data, HIV/CD4 category was strongly associated with new HPV detection: HIV-uninfected as reference, OR, 9.2; 95% CI, 3.2 to 26.4, OR, 5.2; 95% CI, 1.8 to 14.8, and OR, 6.3; 95% CI, 2.0 to 19.3 for HIV-infected CD4 >500, 200 to 500, and <200, respectively. Also associated with the outcome were recent crack use (OR, 1.8; 95% CI, 1.0−3.3) and number of male sex partners in the last 10 years (OR, 1.9; 95% CI, 0.8−4.4 and OR, 2.5; 95% CI, 1.1−6.0 for 0−2 (reference), 3−7, and >7 partners, respectively). These findings were similar to the main analyses presented in Table 2.

Although the numbers for bivariate analyses among strata of HIV serostatus were limited, we noted similarities in kind to the unadjusted results presented in Table 3. For visits from HIV-uninfected women, recent use of marijuana (OR, 9.8; 95% CI, 1.1−88.7), recent injection of both heroin and cocaine (OR 14.8; 95% CI 1.4−155.1), and recent crack use (OR, 12.8; 95% CI, 1.1−148.4) were associated with new HPV detection. Among visits of

HIV-infected women, we observed associations with the outcome for recent crack use (OR, 2.0; 95% CI, 1.0−4.0) and for 1 or more male sex partners reported in the 2 immediately preceding visit intervals (OR, 2.0; 95% CI, 1.1−3.6). No other covariates were significantly associated in either strata of HIV serostatus (data not shown).

DISCUSSION

The objective of this analysis was to explore the potential determinants of newly detected HPV infection among a population of high-risk injection drug using women. Overall, new type-specific HPV infection was detected in 22% of visits. This varied significantly by HIV serostatus (30% vs. 6% for HIV-infected and uninfected, respectively) and by CD4 cell count among HIV-infected participants, which is consistent with previous studies.15−17 Also consistent with the literature, new HPV detection was more common among younger women and those reporting a greater number of male sex partners in the last 10 years.4 Newly detected HPV infection was similarly frequent among women reporting 1 or more male sex partners in the last 6 months and among women reporting sexual abstinence (i.e., no male sex partners in the last 6 months) (22% and 21%, respectively; $P = 0.7$). Analogous observations have been described in other cohorts of high-risk and/or HIV-infected women.7,18

When examining the determinants of newly detected HPV infection among the entire cohort, we observed independent effects for HIV/CD4 cell count and recent crack use. Given the strong effect of HIV/CD4 cell count in the current study and described in the literature, (6 reviewed in16), we then stratified our regression analyses by HIV serostatus. For HIV-uninfected women, recent marijuana use was an independent predictor of new HPV detection (OR, 3.5; 95% CI, 1.3−9.5). This association was also observed in the sensitivity analysis that used a more conservative definition of the outcome (OR, 9.8; 95% CI, 1.1−88.7). Although scientific literature regarding HPV infection and marijuana use is limited, one cross-sectional study reported an odds ratio of 5.2; 95% CI, 1.2 to 2.2 for smoking marijuana and/or related products for the outcome of prevalent HPV DNA detection.19 Another study found that its statistically significant association between marijuana use and HPV infection became attenuated upon adjustment for multiple sex partners,20 although that was not the case in our analyses. It is interesting to note that this nonsexual factor and others, including recent smoking and crack use, seemed more strongly associated with the outcome relative to sexual factors, including number of male sex partners in the last 6 months and high-risk sex in the last 6 months. For HIV-infected women, CD4 cell count category and number of male sex partners in the last 6 months were the independent predictors of newly detected HPV infection. In the final multivariate model, other covariates (e.g., age category, crack use in last 6 months, antiretroviral therapy in the last 6 months) showed borderline statistical significance as predictors of newly detected HPV infection.

To examine the robustness of our results, we conducted sensitivity analyses. The first suggested less than 30% of the study outcomes [i.e., 1 or more newly detected type-specific HPV infection(s)] could be affected by intervening false-negative HPV results. Although more conservative outcome and sexual exposure definitions limited the data available for analyses, when restricting to only those women with new HPV detected after 2 prior negative visits, we again observed the effect of HIV/CD4 cell count and recent crack use on new HPV detection. Although crack use is generally associated with multiple sex partners and exchanging sex for drugs or money,21 these recent sexual behavior variables (e.g., number of male sex partners in last 6 months, any high-risk sex in last 6 months) did not seem to confound the relationship between crack use and newly detected HPV in the main

analyses. This assumes, of course, that the study's survey questions accurately capture sexual behaviors.

Given newly detected HPV infection in the entire cohort, we observed increased odds of recent crack use (OR, 1.7; 95% CI, 1.1−2.6). We also found that crack use was associated with Pap abnormality among visits from HIV-infected women with the lowest CD4 cell counts (<200 per mm^3) (OR, 2.4; 95% CI, 1.1−5.1). These findings are consistent with a recently published study conducted among a similar high-risk population. Minkoff et al. reported that recent crack/cocaine use was associated with increased risk of incident HPV (and cervical squamous intraepithelial lesion) detection (HR, 1.20; 95% CI, 1.02−1.42) among injection drug using women with or at high risk of HIV infection.22 These data raise the possibility that crack use may be mediating an HIV-independent immunosuppressive cervical microenvironment, as has been suggested for cigarette smoking.23 In fact, our data also suggest a positive association of cigarette smoking and new HPV detection, particularly among the HIV-uninfected participants (OR, 3.4; 95% CI, 0.4−26.3); however, because 87% of study participants were smokers, we had limited power to detect significant effects. Opiates and cocaine have been shown to be associated with decreased lymphoproliferative responses *in vitro* (reviewed in24). More specific investigation regarding the effect of drug use on genital tract immunity is needed, particularly regarding the possible increase risk of sexual transmission of HIV.

Newly detected HPV infection was as frequent among women reporting 1 or more male sex partners in the last 6 months as among those reporting sexual abstinence. This could suggest alternative determinants of new HPV detection. Other cohorts of high-risk and/or HIV-infected women report comparable findings and suggested sources such as autoinoculation from other genital sites, transmission by fomites, and reactivation of latent/previously-acquired HPV infection25 (reviewed in15). The reactivation explanation is supported by the effects of HIV-, transplant-, and pregnancy-associated immunosuppression on the natural history of HPV infection,26،27 as well the etiology of recurrent respiratory papillomatosis disease28 and animal models of papillomavirus infection.29

Although our cohort study has 5 years of prospective data, comprehensive HPV genotyping, and pre-HAART follow-up of HIV-infected women, it is not without limitations. This was a secondary data analysis of a substudy contained within a larger cohort that focuses on the natural history of HIV infection. We lacked HIV RNA viral load data, which would have allowed us to incorporate effects of virologic suppression. Given the predominantly middle-aged structure of the study population, we lacked power to adequately assess new HPV detection among menopausal women. Participants were predominantly black injection drug users in an urban living environment, many of whom were HIV-infected, consequently the results of this study may not be generalizable to other populations.

Larger studies of HIV-uninfected injection drug users are needed to more fully characterize the determinants of newly detected HPV infection among high-risk women. HIV-associated immunosuppression may mask the effects of nonsexual determinants of new HPV infection, such as crack and marijuana use. Further, these results provide additional evidence that HPV infection may occur in the absence of recent sexual activity. Reactivation of previously acquired HPV infection would have public health implications for HPV vaccination strategies30 and cervical cancer screening algorithms, especially among immunocompromised or high-risk individuals, like injection drug users, who may be less likely to participate in cervical cancer screening programs.

Although the data presented here were collected in the late 1980s and mid 1990s, our findings are still relevant to today's drug using women and women with or at risk for HIV

infection. For the high-risk population in the current study, new HPV detection was associated with recent use of crack and marijuana, independent from recent opportunity for sexual exposure. This may lead to additional risk of HPV infection and persistence among women who likely have limited access to medical care. Although there has been an increasing national substance abuse trend of noninjection drug use (e.g., crack, methamphetamines), this has not been observed to the same degree in Baltimore, MD, where the types and use of drugs have been relatively stable. The ALIVE study has reported, though, decreasing trends of high-risk behavior and HIV incidence among its injection drug users.31 Much like within the larger United States, the injection drug using population in Baltimore is aging.32 This, in combination with increased survival due to HAART therapy, presents new public health challenges for preventing morbidity and mortality among these high-risk populations.

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TABLE 1

Selected Characteristics of Injection Drug Using Women at Enrollment in the Gynecological Substudy of ALIVE in Baltimore, Maryland, 1992−1997

Characteristic	HIV-Uninfected n (%)	HIV-Infected N = 146 n (%)	*P**
Race			
Black, non-Hispanic, and Hispanic	68 (93)	140 (96)	0.38
White, non-Hispanic	5 (7)	6 (4)	
Age (yrs)			
<35	20 (27)	58 (40)	0.12
35−39	22 (30)	48 (33)	
40−45	20 (27)	28 (19)	
>45	11 (15)	12 (8)	
Cigarette smoking in last 6 mo			
Yes	61 (84)	130 (91)	0.11
Among smokers, packs/d in last 6 mo			
<1	26 (43)	47 (36)	0.39
≥1	35 (57)	83 (64)	
Crack use in last 6 mo			
Yes	17 (23)	38 (26)	0.67
Injection drug use in last 6 mo			
Injection of heroin only			
Yes	30 (39)	75 (46)	0.32
Injection of cocaine only			
Yes	24 (32)	68 (42)	0.13
Injection of both heroin and cocaine			
Yes	21 (28)	53 (33)	0.43
Marijuana use in last 6 mo			
Yes	22 (29)	42 (26)	0.62
Alcohol in last 6 mo			
Yes	40 (55)	85 (58)	0.63
Ever oral contraceptive use†			
Yes	45 (62)	85 (58)	0.84
High-risk sex‡ in last 6 mo			
Yes	31 (42)	49 (34)	0.20
No. male sex partners in last 6 mo			
0	16 (22)	44 (30)	0.19
1	47 (64)	75 (51)	
>1	10 (14)	27 (19)	
No. male sex partners in last 10 yrs†			
0−2	28 (38)	26 (18)	0.01
3−7	29 (40)	61 (42)	

Characteristic	HIV-Uninfected n (%)	HIV-Infected N = 146 n (%)	P*
>7	14 (19)	42 (29)	
No. live births in lifetime†			
0−1	23 (32)	43 (29)	0.92
2	17 (23)	28 (19)	
>2	28 (38)	46 (32)	
CD4 category (cells/mm^3)			
>500	N/A	63 (43)	N/A
200−500		52 (36)	
<200		30 (21)	
HIV treatment in last 6 mo			
None	N/A	82 (56)	N/A
Mono-therapy		56 (38)	
Dual-therapy		7 (5)	
HAART		1 (1)	

Percentages may not sum to 100% due to missing data.

HIV indicates human immunodeficiency virus; HAART, highly active antiretroviral therapy; N/A, not applicable.

*χ^2 test for heterogeneity between HIV serogroups.

†Assessed at baseline enrollment in the parent study, ALIVE.

‡High-risk sex is defined as anonymous and/or traded sex, sex with multiple partners without always using condom, and/or sex with injection drug user(s) without always using condom.

TABLE 2

Odds Ratios Given New HPV Detection Among Injection Drug Using Women

Covariate	Entire Cohort (N = 775 Visits)		
	n	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Age category (yrs)			
<35 (reference)	195	1.0	1.0
35−39	227	0.9 (0.5−1.4)	1.0 (0.6−1.6)
40−445	205	0.6 (0.3−1.0)	0.6 (0.4−1.1)
>45	148	0.5 (0.3−0.9)	0.7 (0.4−1.4)
HIV/CD4 category (cells/mm^3)			
HIV-uninfected (reference)	273	1.0	1.00
HIV-infected/CD4 >500	149	5.4 (2.8−10.6)	4.6 (2.3−8.9)
HIV-infected/CD4 200−500	214	6.5 (3.4−12.3)	5.4 (2.8−10.3)
HIV-infected/CD4 <200	136	10.8 (5.4−21.5)	10.9 (5.5−21.7)
Smoking in last 6 mo	667	1.8 (0.8−4.0)	—
Crack use in last 6 mo	185	1.3 (0.9−1.9)	1.7 (1.1−2.6)
Injection drug use in last 6 mo			
Injection of heroin only	290	0.8 (0.6−1.2)	—
Injection of cocaine only	268	1.1 (0.7−1.6)	—
Injection of both heroin and cocaine	202	1.0 (0.7−1.6)	—
Marijuana use in last 6 mo	225	1.1 (0.7−1.7)	—
Ever oral contraceptive use†	492	1.0 (0.6−1.6)	—
Any STD in last 6 mo	103	1.6 (0.9−2.7)	—
High-risk sex‡ in last 6 mo	150	0.8 (0.5−1.3)	—
No. male sex partners in last 6 mo			
0 (reference)	307	1.0	—
1	370	1.2 (0.8−1.7)	—
>1	97	0.8 (0.4−1.5)	—
No. male sex partners in last 10 yr†			
0−2 (reference)	210	1.0	1.0
3−7	312	1.7 (0.9−3.0)	1.3 (0.7−2.3)
>7	204	2.2 (1.2−4.1)	1.4 (0.8−2.6)
No. live births in lifetime†			
0−1 (reference)	243	1.0	—
2	146	0.6 (0.3−1.3)	—
>2	295	0.9 (0.5−1.5)	—

HIV indicates human immunodeficiency virus; OR, odds ratio; CI, confidence interval; STD, sexually transmitted disease.

*Adjusted for HIV/CD4, age category, crack use in last 6 months, and number of male sex partners in last 10 years.

†Assessed at baseline enrollment in the parent study, ALIVE.

‡High risk sex is defined as anonymous and/or traded sex, sex with multiple partners without always using condom, and/or sex with injection drug user(s) without always using condom.

TABLE 3

Odds Ratios Given New HPV Detection Stratified by HIV Status Among Injection Drug Using Women

Covariate	HIV-Uninfected (N = 273 visits)			HIV-Infected (N = 502 visits)		
	n	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)	n	Unadjusted OR (95% CI)	Adjusted† OR (95% CI)
Age category (yrs)						
<35 (reference)	41	1.0	1.0	154	1.0	1.0
35−39	90	0.9 (0.2−4.4)	0.8 (0.1−4.4)	137	1.0 (0.6−1.7)	1.1 (0.6−1.7)
40−445	69	0.4 (0.1−2.6)	0.4 (0.1−1.8)	136	0.6 (0.4−1.1)	0.6 (0.3−1.0)
>45	73	1.2 (0.2−6.4)	0.9 (0.2−4.9)	75	0.5 (0.3−1.1)	0.5 (0.3−1.1)
CD4 category (cells/mm^3)						
>500 (reference)	263	N/A	N/A	149	1.0	1.0
200−500	9			214	1.2 (0.7−2.0)	1.2 (0.7−2.0)
<200	0			136	2.0 (1.1−3.5)	2.0 (1.1−3.6)
Smoking in last 6 mo	224	3.4 (0.4−26.3)	—	443	1.4 (0.6−3.2)	—
Crack use in last 6 mo	80	2.2 (0.9−5.5)	—	105	1.6 (1.0−2.5)	1.5 (1.0−2.4)
Injection drug use in last 6 mo						
Injection of heroin only	100	1.7 (0.5−5.4)	—	190	0.8 (0.5−1.1)	—
Injection of cocaine only	82	3.4 (1.0−11.2)	1.7 (0.2−18.1)	186	0.8 (0.5−1.3)	—
Injection of both heroin and cocaine	61	3.7 (1.1−12.2)	1.8 (0.2−17.7)	141	0.8 (0.5−1.3)	—
Marijuana use in last 6 mo	96	4.5 (1.7−11.7)	3.5 (1.3−9.5)	129	1.1 (0.6−1.8)	—
Ever oral contraceptive use‡	178	2.3 (0.7−8.2)	—	314	0.9 (0.5−1.5)	—
Any STD in last 6 mo	28	1.3 (0.2−7.6)	—	75	1.6 (0.9−2.8)	—
High–risk sex§ in last 6 mo	88	0.9 (0.3−2.4)	—	62	1.3 (0.7−2.4)	—
No. male sex partners in last 6 mo						
0 (reference)	69	1.0	1.0	238	1.0	1.0
1	144	0.6 (0.1−3.4)	0.5 (0.1−3.7)	226	1.6 (1.1−2.3)	1.6 (1.1−2.4)
>1	60	2.0 (0.5−8.2)	1.2 (0.3−5.3)	37	1.0 (0.5−2.3)	0.9 (0.4−2.1)
No. male sex partners in last 10 yrs‡						
0−2 (reference)	104	1.0	—	106	1.0	—
3−7	109	0.7 (0.2−2.5)	—	203	1.6 (0.8−3.1)	—
>7	54	0.8 (0.2−4.3)	—	150	1.9 (1.0−3.7)	—

Covariate	HIV-Uninfected (N = 273 visits)			HIV-Infected (N = 502 visits)		
	n	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)	n	Unadjusted OR (95% CI)	Adjusted† OR (95% CI)
No. live births in lifetime‡						
0−1 (reference)	93	1.0	—	150	1.0	—
2	65	1.6 (0.3−8.6)	—	81	0.6 (0.3−1.2)	—
>2	102	1.9 (0.5−7.4)	—	193	0.8 (0.4−1.4)	—
Any antiretroviral therapy in last 6 mo	0	N/A	N/A	205	1.5 (1.0−2.2)	1.5 (1.0−2.3)

HIV indicates human immunodeficiency virus; OR, odds ratio; CI, confidence interval; STD, sexually transmitted disease; N/A, not applicable.

*HIV-uninfected adjustment: age category, injection of cocaine only in last 6 months, injection of both heroin and cocaine in last 6 months, marijuana use in last 6 months, number of male sex partners in last 6 months.

†HIV-infected adjustment: age category, CD4 cell count category, crack use in last 6 months, number of male sex partners in last 6 months, any antiretroviral therapy in last 6 months.

‡Assessed at baseline enrollment in the parent study, ALIVE.

§High risk sex is defined as anonymous and/or traded sex, sex with multiple partners without always using condom, and/or sex with injection drug user(s) without always using condom.