Title

Risk of Cervical Precancer and Cancer Among HIV-Infected Women With Normal Cervical Cytology and No Evidence of Oncogenic HPV Infection

Journal

JAMA, 308(4)

ISSN

0098-7484

Authors

Keller, Marla J
Burk, Robert D
Xie, Xianhong
et al.

Publication Date

2012-07-25

DOI

10.1001/jama.2012.5664

Peer reviewed

Published in final edited form as:
JAMA. 2012 July 25; 308(4): 362–369. doi:10.1001/jama.2012.5664.

Risk of Cervical Pre-Cancer and Cancer Among HIV-Infected Women With Normal Cervical Cytology and No Evidence of Oncogenic HPV Infection

Marla J. Keller, MD[1], **Robert D. Burk, MD**[1], **Xianhong Xie, PhD**[1], **Kathryn Anastos, MD**[1], **L. Stewart Massad, MD**[2], **Howard Minkoff, MD**[3], **Xiaonan Xue, PhD**[1], **Gypsyamber D'Souza, PhD**[4], **D. Heather Watts, MD**[5], **Alexandra M. Levine, MD**[6], **Philip E. Castle, PhD**[7], **Christine Colie, MD**[8], **Joel M. Palefsky, MD**[9], and **Howard D. Strickler, MD, MPH**[1]

[1]Albert Einstein College of Medicine, Bronx, NY

[2]Washington University School of Medicine, St. Louis, MO

[3]Maimonides Medical Center, Brooklyn, NY

[4]Johns Hopkins School of Public Health, Baltimore, MD

[5]National Institute of Child Health and Human Development, Bethesda, MD

[6]City of Hope National Medical Center, Duarte, CA

[7]American Society for Clinical Pathology, Washington, DC

[8]Georgetown University Medical Center, Washington, DC

[9]University of California, San Francisco, CA

Abstract

Context—U.S. cervical cancer screening guidelines for HIV-uninfected women 30 years of age and older have recently been revised, increasing the suggested interval between Pap tests from three years to five years among those with normal cervical cytology (the Pap test) who test negative for oncogenic human papillomavirus (HPV). Whether a three-year or five-year screening interval might be used in HIV-infected women who are cytologically normal and oncogenic HPV-negative is unknown.

Corresponding author: Dr. Marla Keller, Department of Medicine, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Mazer Building, Room 512, Bronx, New York, 10461 USA, Telephone: 718-430-3240, Fax: 718-430-8879, marla.keller@einstein.yu.edu..

Author Contributions: Dr. Strickler had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Keller, Strickler, Burk, Palefsky, Massad. *Acquisition of data:* Burk, Palefsky, Massad, Anastos, Minkoff, Levine, Strickler. *Analysis and interpretation of data:* Keller, Burk, Palefsky, Massad, Xue, Xie, Colie, Castle, Watts, D'Souza, Strickler. *Drafting of the manuscript:* Keller, Strickler, Xue, Xie, Massad. Critical revision of the manuscript or important intellectual content: Keller, Burk, Palefsky, Massad, Castle, Anastos, Minkoff, Levine, Watts, Xue, Xie, Colie, D'Souza, Strickler. *Statistical analysis:* Keller, Xue, Xie, Strickler. *Obtained funding:* Strickler, Burk, Palefsky, Anastos, Minkoff, Levine. *Administrative, technical, or material support:* Strickler, Burk, Palefsky, Castle, Colie, Watts, D'Souza. *Study supervision:* Strickler, Burk, Palefsky, Anastos, Minkoff, Levine.

Financial Disclosures: Dr. Palefsky reports receiving grant support through his institution, travel support, and fees for review activities through his institution from Merck Sharp & Dohme, serving as a board member and consultant and providing expert testimony for Merck Sharp & Dohme and receiving fees for these activities through his institution, and serving as a member of the scientific advisory board of Pharmajet. Dr. Castle reports receiving fees from Merck Sharp & Dohme for serving as a member of a Data and Safety Monitoring Board.

Previous Presentation: Oral presentation at the 2011 International Papillomavirus Conference, Berlin, Germany, 2011.

Objective—To determine the risk of cervical pre-cancer or cancer defined cytologically (high-grade squamous intraepithelial lesions or greater [HSIL+]) or histologically (cervical intraepithelial neoplasia 2 or greater [CIN-2+]), as two separate endpoints, in HIV-infected women and HIV-uninfected women who at baseline had a normal Pap test and were negative for oncogenic HPV.

Design, Setting and Participants—Participants included 420 HIV-infected women and 279 HIV-uninfected women with normal cervical cytology at their enrollment in a multi-institutional cohort, between October 1, 2001 and September 30, 2002, with follow-up through April 30, 2011. Clinical sites were in the Bronx, Brooklyn, Chicago, Los Angeles, San Francisco, and Washington, DC. Semi-annual visits included Pap testing and, if indicated, cervical biopsy. Cervicovaginal lavage specimens from enrollment were tested for HPV DNA using PCR. The primary analysis was truncated at five years of follow-up.

Main Outcome Measure—The five-year cumulative incidence of cervical pre-cancer and cancer.

Results—No oncogenic HPV was detected in 369 (88%; 95% CI, 84%-91%) of the HIV-infected women and 255 (91%; 95% CI, 88%-94%) of the HIV-uninfected women with normal cervical cytology at enrollment. Among these oncogenic HPV-negative women two cases of HSIL + were observed; an HIV-uninfected woman and an HIV-infected woman with a CD4 cell count of 500/μL or greater. Histologic data were obtained from four of the six sites. There were six cases of CIN-2+ in N=145 HIV-uninfected women (cumulative incidence = 5% [95% CI, 1%-8%]) and nine cases in N=219 HIV-infected women (cumulative incidence = 5% [95% CI, 2%-8%]). This included one case of CIN-2+ in N=44 oncogenic HPV-negative HIV-infected women with CD4 cell counts less than 350/μL (cumulative incidence = 2% [95% CI, 0%-7%]), one case in N=47 women with CD4 cell counts of 350 to 499/μL (cumulative incidence = 2% [95% CI, 0%-7%]), and seven cases in N=128 women with CD4 cell counts of 500/μL or greater (cumulative incidence = 6% [95% CI, 2%-10%]). One HIV-infected and one HIV-uninfected woman had CIN-3, but none had cancer.

Conclusion—The five-year cumulative incidence of HSIL+ and CIN-2+ was similar in HIV-infected women and HIV-uninfected women who were cytologically normal and oncogenic HPV-negative at enrollment.

Introduction

In an approach termed HPV co-testing, cervical cancer screening guidelines in the United States endorse the use of oncogenic human papillomavirus (HPV) DNA testing concurrent with cervical cytology in HIV-uninfected women aged 30 years or older .[1,2] According to these guidelines, women with a normal Pap test but who test positive for oncogenic HPV should be re-screened in one year, whereas the recommended interval for re-screening in those who are oncogenic HPV-negative was recently increased from three years[3] to five years.[1,2] These recommendations reflect the low risk of cervical pre-cancer and cancer observed in cytologically normal, oncogenic HPV-negative women during long term follow-up studies (as recently reviewed by Whitlock et al, 2011)[4], and modeling studies which found that HPV co-testing at three and five year intervals provided similar outcomes as annual conventional Pap tests.[5]

HPV co-testing, however, is not currently recommended as part of cervical cancer screening in HIV-infected women,[6] nor was this issue addressed in the updated screening guidelines.[1,2] Current recommendations are for HIV-infected women who have initiated sexual intercourse to have two Pap tests at 6 month intervals in the first year following diagnosis of HIV infection and, if normal, then on an annual basis.[6] Only one study in HIV-infected women to our knowledge prospectively examined the risk of incident cervical pre-

cancer and cancer following a normal Pap test and a negative oncogenic HPV DNA test. That study in the Women's Interagency HIV Study (WIHS), a large prospective cohort of HIV-infected women and HIV-uninfected women, measured the cumulative incidence of any squamous intraepithelial lesion (SIL), and high-grade SIL or greater (HSIL+), according to baseline HPV DNA results. No cases of HSIL were observed through three years of follow-up and no cancers were diagnosed for up to seven years among 412 cytologically normal, HPV-negative HIV-infected women.[7]

Women in this earlier study, however, were enrolled during 1994-1995, prior to the widespread use of highly active antiretroviral therapy (HAART), which began in late 1996, and most remained HAART naïve for the first several years of the study. Approximately 20% had a CD4 cell count less than 200/μL. Further, that study was limited by the absence of histologic results, the major clinical criteria used to determine the need for cervical treatment. Therefore, the current investigation examined the three-year and five-year risk of cervical pre-cancer and cancer defined by cytology (i.e., HSIL+) and histology (cervical intraepithelial neoplasia 2 or greater [CIN-2+]), each as its own endpoint, in a separate cohort of HIV-infected women and HIV-uninfected women enrolled in the WIHS during 2001-2002. The HIV-infected women in the 2001-2002 cohort were shown to be representative of U.S. women with HIV/AIDS.[8]

Methods

Participants and Specimens

The WIHS is an ongoing geographically and ethnically diverse prospective cohort study of HIV-infected women and HIV-uninfected women enrolled through similar clinical and outreach sources at each of six clinical consortia located in the Bronx, Brooklyn, Chicago, Los Angeles, San Francisco and Washington, DC.[9] The initial enrollment was conducted between October 1, 1994 and November 15, 1995 (N=2059 HIV-infected women and N=569 HIV-uninfected women), and a second enrollment was separately conducted between October 1, 2001 and September 30, 2002 (N=737 HIV-infected women and N=406 HIV-uninfected women).[8,9] Interviewer administered questionnaires are completed at each semi-annual visit and include information regarding age, race/ethnicity (i.e., Black, White, Hispanic, Asian, American Indian, Alaskan Native, Other), additional demographic variables, medical history, and risk behaviors. The HIV-infected women in the 2001-2002 cohort were shown to be similar to AIDS cases among U.S. women nationwide reported by the Centers for Disease Control and Prevention (CDC) in 2001, in terms of their racial distribution, other demographic factors, and CDC-defined HIV exposure category.[8]

At all semi-annual visits participants had a Pap test and a cervicovaginal lavage (CVL) for HPV DNA testing. Pap tests were interpreted centrally according to the 2001 Bethesda System.[10] Colposcopy is recommended for a cytologic diagnosis of atypical squamous cells of undetermined significance (ASC-US) or greater. Cytologic data for the current study were obtained from all WIHS sites, whereas colposcopic and histologic data were obtained from four designated WIHS sites, chosen based on their facilities and clinician training; Brooklyn, Chicago, Los Angeles, San Francisco. Written informed consent was obtained from all participants and the project was approved by each local IRB. Data were available through April 30, 2011.

Laboratory Testing

HPV DNA was detected with L1 consensus primer MY09/MY11/HMB01 polymerase chain reaction assays. Primer set PC04/GH20, which amplifies a 268-base-pair cellular β-globin DNA fragment, was included in each assay as an internal control to assess the adequacy of

amplification. Details of these methods have been previously reported[11,12] and the results were shown to have high sensitivity and specificity.[13-15] Within the WIHS itself these assays have been shown to have high inter-laboratory reproducibility.[13] Briefly, after proteinase K digestion, 2-10 μL of each cell digest was used in reaction mixtures containing 10 mM Tris-HCl, 50 mM KCl, 4 mM $MgCl_2$, all four deoxyribonucleotide triphosphates (each at 200 μM), 2.5 U of AmpliTaq DNA polymerase, and 0.5 μM of each primer. There were 35 amplification cycles (95°C for 20 seconds, 55°C for 30 seconds, and 72°C for 30 seconds), with a 5-minute extension period at 72°C on the last cycle. Amplification products were probed for the presence of any HPV DNA with a generic probe mixture and probed for HPV DNA with filters individually hybridized with type-specific biotinylated oligonucleotide probes for more than 40 individual HPV types.[11,12] The HPV types defined as oncogenic were 16/18/31/33/35/39/45/51/52/56/58/59/68/73/82, and other HPV types were considered non-oncogenic.[16,17]

Statistical Methods

Initial descriptive analyses contrasted the characteristics of the HIV-infected women and HIV-uninfected women in this study, using the t-test (means), Wilcoxon test (median), or Pearson's chi-square test (proportions). For the oncogenic HPV-negative women, standard life-table methods were used to estimate the cumulative incidence of SIL and CIN, with 95% confidence limits (a measure of the precision of each estimate) calculated based on the life-table estimator under a normal approximation assumption. The CD4 cell count was used to stratify HIV-infected participants in preference to HIV viral load, since CD4 cell count but not HIV viral load has been associated with risk of incident invasive cervical cancer.[18,19] In keeping with cervical cancer screening guidelines, our main analyses examined both three-year and five-year cumulative incidence. Participants who had a hysterectomy or reported cervical treatment were censored at the visit before their procedure. In life-table analysis censoring is assumed to occur uniformly throughout each interval.[20] Therefore, to determine the overall follow-up rate in HPV-negative women at five years of observation, the effective sample size (the numerator) was calculated based on the number of women entering year 5 (which reflects all attrition that came before that final year) minus half of those who during that last year were censored. Cases were not considered censored, and were included in the numerator. The overall follow-up rate was then this numerator divided by the number of women at the start of the study.[20] Given the low event rate, the main analyses used all available data and assumed that disease status did not change during intervals of missing data. To assess this assumption, however, in additional analyses, participants who for any reason had missing data for greater than one year were censored at the time of their last visit with complete data. As this affected less than an average of 1.6% of participants annually and did not alter the findings we elected to report herein the life-table results calculated without this additional censoring. The results censored for missing data are reported in eTable 1 and eTable 2 in the eAppendix (available at http://www.jama.com). The extent of missing data is shown in the footnotes of the life-tables. Statistical significance was defined as $P<.05$ determined using two-sided tests. All analyses were conducted using SAS software version 9.1.3 (SAS Institute, Cary, NC), except where indicated.

Results

Study Participants

There were 505 HIV-infected women and 345 HIV-uninfected women with normal cervical cytology at enrollment. Women were excluded from analysis if (i) their baseline HPV or CD4 cell count data were missing (N=52 HIV-infected women and N=31 HIV-uninfected women); (ii) the cervix had been removed prior to enrollment (N=15 and N=7); (iii) follow-

up data were unavailable (N=18 and N=27); or (iv) HIV seroconversion occurred during follow-up (N=1). In total, 420 HIV-infected women and 279 HIV-uninfected women were included in the current analysis. Table 1 shows selected baseline characteristics of these women. The HIV-infected women were modestly older and more likely to be Hispanic than the HIV-uninfected women. Nearly half (47%) of the HIV-infected women were receiving HAART and 56% had a CD4 cell count of 500/μL or greater. Although HIV-infected women reported less recent sexual activity, they were more likely than HIV-uninfected women to test positive for any HPV DNA (32% versus 22%; P=.02). Among HIV-infected women, the prevalence of any HPV DNA and of oncogenic HPV DNA increased with decreasing CD4 cell count (both P-trend ≤.004); ie, the prevalence was 25% for any HPV and 8% for oncogenic HPV in HIV-infected women with CD4 cell counts of 500/μL or greater; 34% and 17%, respectively, for those with CD4 cell counts of 350 to 499/μL; and 47% and 18%, respectively, for those with CD4 cell counts of less than 350/μL.

Overall, no oncogenic HPV was detected in 369 (88%; 95% CI, 84%-91%) of the HIV-infected women and 255 (91%; 95% CI, 88%-94%) of the HIV-uninfected women with normal cervical cytology at enrollment. We measured the cumulative incidence of cervical pre-cancer and cancer in oncogenic HPV-negative women using cytology (HSIL+) and histology (CIN-2+) as separate endpoints.

Through the first five years of observation there were a total of 3281 person-visits of observation in HIV-infected women and 2242 person-visits in HIV-uninfected women, with a median follow-up time of 4.9 years. Figure 1a shows censoring due to treatment or loss to follow-up in these women by year and HIV status. Six women who had a hysterectomy and 115 women who reported other cervical treatment (N=69 HIV-infected women and N=46 HIV-uninfected women) during follow-up were censored at the visit before their procedure. Loss to follow-up averaged 3.6% per year in HIV-infected women and 3.1% in HIV-uninfected women. In life-table analysis all censoring is assumed to occur uniformly throughout each interval (see Statistical Methods). Overall, in the analysis of HSIL+, 70% (effective sample size 218 + 1 case) of the 255 HIV-uninfected women and 67% (effective sample size 245 non-cases + 1 case) of the 369 HIV-infected women contributed five years of observation. The corresponding rates of follow-up at 3 years of observation were 86% and 81%, respectively.

Four of the six sites provided colposcopy and histologic data for the analysis of CIN-2+. The baseline characteristics of these women were similar to all cytologically normal participants in this study (eTable 3). Colposcopy results were obtained in 87% of HIV-infected women (85% of ASC-US, 93% of low grade SIL [LSIL], 100% of HSIL) and 82% of HIV-uninfected women (83% of ASC-US, 80% of LSIL, 100% of HSIL) with a subsequent abnormal Pap test. Loss to follow-up was similar to that observed in all participants (above), 2.9% per year in HIV-infected women and 2.9% in HIV-uninfected women (Figure 1b). In total, 82% (113 non-cases + 6 cases) of 145 HIV-uninfected women and 78% (162 non-cases + 9 cases) of 219 HIV-infected women contributed five years of observation to the analysis of CIN-2+. The corresponding rates of follow-up at 3 years of observation were 92% and 88%, respectively.

Cumulative Incidence of Pre-Cancer

Table 2 and Table 3 show the data for cytology and histology, respectively. Two cases of HSIL+ were observed during the five years of observation (Table 2); one among the HIV-uninfected women and one among the HIV-infected women with a CD4 cell count of 500/μL or greater. Overall, the cumulative incidence of HSIL+ was 0.3% (95% CI, 0%-0.9%) in HIV-infected women and 0.4% (95% CI, 0%-1.3%) in HIV-uninfected women. Similarly, there were few cases of CIN-2+ (Table 3). Based on a total of 15 cases, the cumulative

incidence of CIN-2+ over five years of follow-up was 2% (95% CI, 0%-7%) in HIV-infected women with CD4 cell counts less than 350/μL, 2% (95% CI, 0%-7%) in those with CD4 cell counts of 350 to 499/μL, 6% (95% CI, 2%-10%) in HIV-infected women with CD4 cell counts of 500/μL or greater, and 5% (95% CI, 1%-8%) in HIV-uninfected women. Given the concordance of the findings across CD4 cell count strata we combined the data among HIV-infected women. The overall five-year cumulative incidence of CIN-2+ in HIV-infected women was 5% (95% CI, 2%-8%). Of the CIN-2+ cases, two were CIN-3 (an HIV-infected woman with a CD4 cell count at baseline of 350-499/μL, and an HIV-uninfected woman). The overall five-year cumulative incidence of CIN-3+ was 0.5% (95% CI, 0%-2%) in HIV-infected women and 0.7% (95% CI, 0%-2%) in HIV-uninfected women. No cancers were observed.

Although the five-year cumulative incidence rate of CIN-2+ was estimated to be 5% in both HIV-infected women and HIV-uninfected women, we examined to what extent their true values could be different. Specifically, we calculated the upper and lower confidence limits for these data; an estimated difference of 0% (95% CI, −4%–5%). A similar analysis was conducted for HSIL+. As reported above, the cumulative incidence of HSIL+ in HIV-infected women and HIV-uninfected women was 0.3% and 0.4%, respectively, and the calculated difference was −0.1% (95% CI, −0.9%–0.9%). Interestingly, unlike with HSIL+, the cumulative incidence of any SIL differed by host immune status (Table 2). HIV-infected women with CD4 cell counts less than 350/μL had a five-year cumulative incidence of any SIL of 25% (95% CI, 13%-34%), whereas it was 11% in each of the other two HIV-infected groups and 6% in HIV-uninfected women. The cumulative incidence of any CIN did not vary substantially by HIV-serostatus or CD4 cell count (Table 3).

Data from follow-up visits beyond five years of observation are also of interest but need to be addressed conservatively, since there was continued incremental loss to follow-up; an average of 4.0% and 3.4% per year, respectively, for HSIL+ and CIN-2+ (eTables 4-7). Most notably, no cases of invasive cancer were detected during all nine years of observation. There was one case of CIN-3 in an HIV-infected woman with a CD4 cell count of 500/μL or greater, which occurred between eight and nine years of follow-up, and one case of HSIL involving an HIV-uninfected woman diagnosed between six and seven years of follow-up. Of the five cases of CIN-2 that were observed after five years of follow-up, three occurred among HIV-infected women with a CD4 cell count of 500/μL or greater, one among those with a CD4 cell count of 350 to 499/L, and one in an HIV-uninfected woman. Overall, the seven year cumulative incidence of CIN-2+ was 6% (95% CI, 2%-9%) in HIV-infected women and 5% (95% CI, 1%-9%) in HIV-uninfected women, whereas it was 8% (95% CI, 3%-12%) and 5% (95% CI, 1%-9%), respectively, after nine years of observation. For CIN-3+, the cumulative incidence rates were 2% (95% CI, 0%-4%) and 0.7% (95% CI, 0%-2%), respectively, after nine years of observation.

Comment

This study found similar risk of cervical pre-cancer and cancer in HIV-infected women and HIV-uninfected women who had normal cervical cytology and a negative test for oncogenic HPV DNA at enrollment. Specifically, through five years of follow-up, we observed no meaningful differences in the cumulative incidence of HSIL+ or CIN-2+ between HIV-uninfected women and HIV-infected women, regardless of CD4 cell count in this cohort. Based on our analyses, few cases of cervical pre-cancer would have gone undiagnosed had the HIV-infected women we studied not had any additional Pap tests for five years following enrollment, and no more than in the HIV-uninfected women. The estimated cumulative incidence of CIN-2+ in HIV-infected women was 5% across the five years of observation, with an upper 95% confidence interval of 8%. Two HIV-infected women had

CIN-3, representing a five-year cumulative incidence of 0.5%. None had cancer through nine years of follow-up.

These results are consistent with those of a prior study in a separate cohort of women enrolled in the WIHS conducted by our research group.[7] That study involved a much larger number of HIV-infected women with low CD4 cell counts, consistent with the fact that the prior cohort was enrolled in 1994-1995, before the widespread use of HAART. Nonetheless, no cases of HSIL+ were detected in HIV-infected women within three years of their normal Pap test and negative HPV DNA results at study entry. While differences in the two cohorts and the absence of histologic data from the earlier study make it inappropriate to combine their data, it is reassuring that both cohort investigations conducted to date found that HIV-infected women who were cytologically normal and oncogenic HPV-negative had similar risk of cervical pre-cancer and cancer as those who were HIV-uninfected.

There are, however, limitations to the current study. Most importantly, the current findings are generalizable only to women who are similar to those in the WIHS; mainly HIV-infected women in long-term follow-up. Second, testing of CVL specimens may have lower sensitivity for detection of oncogenic HPV than does testing of cervical swabs or a cytobrush.[21,22] Our results are therefore likely conservative, since a small improvement in assay sensitivity would likely result in an improvement in the negative predictive value of HPV testing for CIN-2+ in cytologically normal HIV-infected women. There are also unavoidable limitations to life-table analysis. In particular, life-table methods assume non-informative censoring (ie, that the rate of disease in those who were censored is similar to those not censored), and no statistical methods have been developed to estimate exact confidence intervals for cumulative incidence rates when events are rare; albeit, for sample size and event rates in the range we studied the normal approximation has been shown to provide accurate results.[23] It must also be noted that some women with an abnormal Pap test did not follow investigators' recommendations to have colposcopy, and there was no centralized review of histologic specimens. Reassuringly, though, a recent review by an expert pathologist confirmed 25 of 27 CIN-2+ diagnosed in other WIHS women by their local pathologists (personal communication, Teresa Darragh, MD, Professor of Clinical Pathology, UCSF).

In summary, the results of this prospective study suggest that HIV-infected women in long-term clinical follow-up who are cytologically normal and oncogenic HPV-negative have a risk of cervical pre-cancer similar to that in HIV-uninfected women through five years of follow-up. Additional observational studies or a randomized clinical trial may be necessary before clinical guideline committees consider whether to expand current recommendations regarding HPV co-testing to HIV-infected women. More broadly, the current investigation highlights the potential for a new era of molecular testing, including HPV as well as other biomarkers, to improve cervical cancer screening in HIV-infected women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding/Support: Major support for this study, including HPV DNA testing, was provided through R01-CA-085178. Data in this manuscript were collected by the Women's Interagency HIV Study (WIHS) Collaborative Study Group with centers (principal investigators) at New York City/Bronx Consortium (Kathryn Anastos); Brooklyn, NY (Howard Minkoff); Washington, DC Metropolitan Consortium (Mary Young); The Connie Wofsy Study Consortium of Northern California (Ruth Greenblatt); Los Angeles County/Southern California Consortium (Alexandra Levine); Chicago Consortium (Mardge Cohen); Data Coordinating Center (Stephen Gange). The WIHS is funded by the National Institute of Allergy and Infectious Diseases (U01-AI-35004, U01-AI-31834, U01-

AI-34994, U01-AI-34989, U01-AI-34993, and U01-AI-42590 and by the Eunice Kennedy Shriver National Institute of Child Health & Human Development (U01-HD-32632). The study is co-funded by the National Cancer Institute, the National Institute on Drug Abuse, and the National Institute on Deafness and Other Communication Disorders. Funding is also provided by the National Center for Research Resources (UCSF-CTSI Grant Number UL1 RR024131). Additional support provided by R33-AI079763, the Einstein-Montefiore Center for AIDS Research (P30-AI-51519) and Institute for Clinical and Translational Research (UL1 RR025750). The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

Role of the Sponsors: The WIHS is an NIH-funded multicenter cohort study. Thus, the funding sources had a role in the overall WIHS study design, but not the design of the current ancillary study; one co-author, Dr. Watts, is an employee of NICHD/NIH, and as an author had a role in the interpretation of the current data, and she reviewed and approved the current manuscript.

References

1. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society; American Society for Colposcopy and Cervical Pathology; American Society for Clinical Pathology Screening Guidelines for the Prevention and Early Detection of Cervical Cancer. Journal of lower genital tract disease. Mar 13.2012
2. Moyer VA. Screening for Cervical Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. Mar 14.2012
3. Wright TC Jr. Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 consensus guidelines for the management of women with abnormal cervical screening tests. J Low Genit Tract Dis. Oct; 2007 11(4):201–222. [PubMed: 17917566]
4. Whitlock EP, Vesco KK, Eder M, Lin JS, Senger CA, Burda BU. Liquid-Based Cytology and Human Papillomavirus Testing to Screen for Cervical Cancer: A Systematic Review for the U.S. Preventive Services Task Force. Ann Intern Med. Oct 17.2011
5. Stout NK, Goldhaber-Fiebert JD, Ortendahl JD, Goldie SJ. Trade-offs in cervical cancer prevention: balancing benefits and risks. Arch Intern Med. Sep 22; 2008 168(17):1881–1889. [PubMed: 18809815]
6. Center for Disease Control and Prevention. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. MMWR. 2009; 58(No. RR-4)
7. Harris TG, Burk RD, Palefsky JM, et al. Incidence of cervical squamous intraepithelial lesions associated with HIV serostatus, CD4 cell counts, and human papillomavirus test results. JAMA. Mar 23; 2005 293(12):1471–1476. [PubMed: 15784870]
8. Bacon MC, von Wyl V, Alden C, et al. The Women's Interagency HIV Study: an observational cohort brings clinical sciences to the bench. Clin Diagn Lab Immunol. Sep; 2005 12(9):1013–1019. [PubMed: 16148165]
9. Barkan SE, Melnick SL, Preston-Martin S, et al. The Women's Interagency HIV Study. WIHS Collaborative Study Group. Epidemiology. Mar; 1998 9(2):117–125. [PubMed: 9504278]
10. The 2001 Bethesda System: Terminology for reporting results of cervical cytology. JAMA. 2002; 287:2114–2119. [PubMed: 11966386]
11. Burk RD, Ho GY, Beardsley L, Lempa M, Peters M, Bierman R. Sexual behavior and partner characteristics are the predominant risk factors for genital human papillomavirus infection in young women. J Infect Dis. Oct; 1996 174(4):679–689. [PubMed: 8843203]
12. Strickler HD, Burk RD, Fazzari M, et al. Natural history and possible reactivation of human papillomavirus in human immunodeficiency virus-positive women. J Natl Cancer Inst. Apr 20; 2005 97(8):577–586. [PubMed: 15840880]
13. Palefsky JM, Minkoff H, Kalish LA, et al. Cervicovaginal human papillomavirus infection in human immunodeficiency virus-1 (HIV)-positive and high-risk HIV-negative women. J Natl Cancer Inst. Feb 3; 1999 91(3):226–236. [PubMed: 10037100]
14. Qu W, Jiang G, Cruz Y, et al. PCR detection of human papillomavirus: comparison between MY09/MY11 and GP5+/GP6+ primer systems. J Clin Microbiol. Jun; 1997 35(6):1304–1310. [PubMed: 9163434]

15. Jiang G, Qu W, Ruan H, Burk RD. Elimination of false-positive signals in enhanced chemiluminescence (ECL) detection of amplified HPV DNA from clinical samples. Biotechniques. Oct; 1995 19(4):566–568. [PubMed: 8777045]

16. Munoz N, Bosch FX, de Sanjose S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med. Feb 6; 2003 348(6):518–527. [PubMed: 12571259]

17. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens--Part B: biological agents. Lancet Oncol. Apr; 2009 10(4):321–322. [PubMed: 19350698]

18. Guiguet M, Boue F, Cadranel J, et al. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. Lancet Oncol. 2009; 10(12):1152–1159. [PubMed: 19818686]

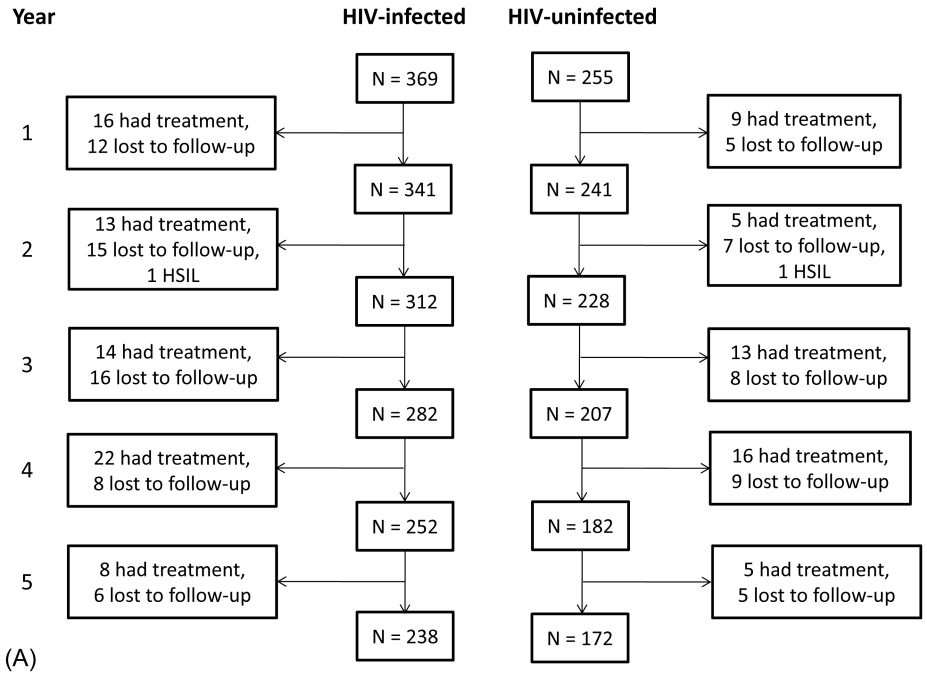
19. Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. J Natl Cancer Inst. 2009; 101(16):1120–1130. [PubMed: 19648510]

20. Leung KM, Elashoff RM, Afifi AA. Censoring issues in survival analysis. Annu Rev Public Health. 1997; 18:83–104. [PubMed: 9143713]

21. Vermund SH, Schiffman MH, Goldberg GL, Ritter DB, Weltman A, Burk RD. Molecular diagnosis of genital human papillomavirus infection: comparison of two methods used to collect exfoliated cervical cells. American journal of obstetrics and gynecology. Feb; 1989 160(2):304–308. [PubMed: 2537011]

22. Wheeler CM, Greer CE, Becker TM, Hunt WC, Anderson SM, Manos MM. Short-term fluctuations in the detection of cervical human papillomavirus DNA. Obstetrics and gynecology. Aug; 1996 88(2):261–268. [PubMed: 8692513]

23. Brown LD, Cai TT, Dasgupta A. Interval estimation for a binomial proportion. Statistical Science. 2001; 16(2):101–133.



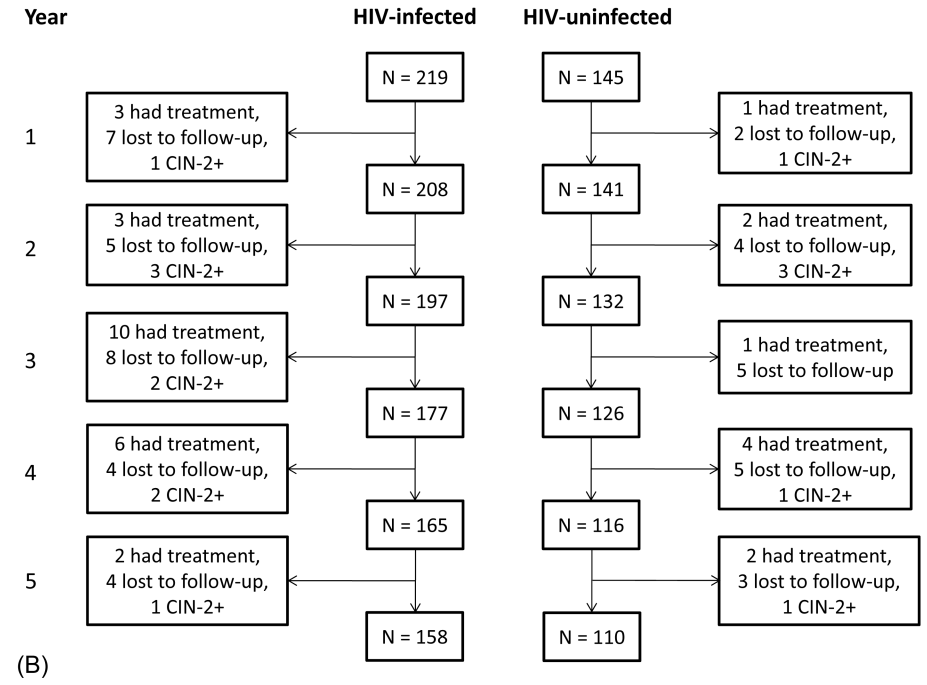


Figure 1.

Censoring among cytologically normal, oncogenic HPV-negative women in the life-table analysis, by year of follow-up and HIV status.

A. Loss to follow-up and censoring for cervical treatment (including hysterectomy) among women in the analysis of HSIL+. In life-table analysis all censoring is assumed to occur uniformly throughout each interval (see Statistical Methods). Thus, in the analysis of HSIL

+, 70% (effective sample size 218 + 1 case) of the 255 HIV-uninfected women and 67% (effective sample size 245 non-cases + 1 case) of the 369 HIV-infected women contributed five years of observation. The corresponding rates of follow-up at 3 years of observation were 86% and 81%, respectively.

B. Loss to follow-up and censoring for cervical treatment among women in the analysis of CIN-2+. In the analysis of CIN-2+, 82% (113 non-cases + 6 cases) of 145 HIV-uninfected women and 78% (162 non-cases + 9 cases) of 219 HIV-infected women contributed five years of observation to the analysis of CIN-2+. The corresponding rates of follow-up at 3 years of observation were 92% and 88%, respectively.

Table 1

Baseline characteristics of HIV-infected and HIV-uninfected women with normal cervical cytology at enrollment during 2001-2002 in the Women's Interagency HIV Study (WIHS)

Characteristic	HIV-infected (n=420)	HIV-uninfected (n=279)	*P*-value[a]
Age, y			
Mean (SD)	34 (7)	30 (8)	<.001
Median (IQR)	33 (28-38)	29 (23-36)	<.001
Race/ethnicity, No. (%)			
Black	222 (53)	159 (57)	.04
Hispanic	150 (36)	75 (27)	
White	31 (7)	33 (12)	
Other	17 (4)	12 (4)	
Smoking, No. (%)			
Never	215 (51)[b]	103 (37)	.0001
Former	58 (14)	35 (13)	
Current	146 (35)	141 (51)	
Alcohol Use, No. (%)			
None	249 (60)	113 (41)	<.0001
Light (<3 drinks/week)	119 (29)	84 (30)	
Moderate (3-13 drinks/week)	32 (8)	53 (19)	
Heavy (>14 drinks/week)	17 (4)	28 (10)	
Injected drugs in the last 6 mo, No. (%)			
Yes	3 (1)	7 (3)	.05
No	416 (99)	272 (97)	
Sexually active in the last 6 mo, No. (%)			
Yes	335 (80)	243 (87)	.01
No	84 (20)	36 (13)	
HPV DNA test results, No. (%)			
Negative	287 (68)	218 (78)	.02
Non-oncogenic	82 (20)	37 (13)	
Oncogenic	51 (12)	24 (9)	
CD4 cell count, cells/μL			

Characteristic	HIV-infected (n=420)	HIV-uninfected (n=279)	*P*-value[a]
<200	23 (5)		
200-349	65 (15)		
350-499	98 (23)		
≥500	234 (56)		
HIV RNA, copies/μL			
>80	161 (39)		
>80-10,000	174 (42)		
>10,000-100,000	68 (16)		
>100,000	10 (2)		
HAART use in past 6 mo, No. (%)			
Yes	199 (47)		
No	221 (53)		

Abbreviations: HPV, human papillomavirus; IQR, interquartile range; SD, standard deviation; HAART, highly active antiretroviral therapy.

[a] *P-value* – two sided t-test (means), Wilcoxon test (median), or Pearson's chi-square test (proportions) comparing HIV-infected and HIV-uninfected women.

[b] Some women were missing data, including smoking (1 HIV-infected), alcohol use (3 HIV-infected and 1 HIV- uninfected), injection drug use (1 HIV-infected), sexual activity (1 HIV-infected), and HIV RNA (7 HIV-infected).

Table 2

Cumulative incidence of any SIL and high-grade SIL or greater (HSIL+) in HIV-infected women and HIV-uninfected women who had normal cervical cytology and tested negative for oncogenic HPV DNA at enrollment[a]

Baseline HIV status and CD4 cell count	Year	No. at Start of Interval[b]	No. of Any New SIL	Any New SIL Cumulative Incidence (95% CI)	No. of New HSIL+
HIV-infected CD4 cell count <350/μL	1	72[c]	4	6 (0-11)[d]	0
	2	65	2	9 (2-15)	0
	3	60	6	18 (8-27)	0
	4	51	2	21 (11-31)	0
	5	47	2	25 (13-34)	0
CD4 cell count 350-499/μL	1	81	0	0 (0)	0
	2	75	1	1 (0-4)	0
	3	69	2	4 (0-9)	0
	4	62	2	7 (1-14)	0
	5	58	2	11 (3-18)	0
CD4 cell count ≥500/μL	1	216	4	2 (0-4)	0
	2	207	6	5 (2-8)	1
	3	193	3	6 (3-10)	0
	4	181	5	9 (5-13)	0
	5	169	3	11 (6-15)	0
HIV-uninfected	1	255	4	2 (0-3)	0
	2	245	4	3 (1-5)	1
	3	233	3	4 (2-7)	0
	4	224	2	5 (2-8)	0
	5	213	1	6 (3-9)	0

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HPV, human papillomavirus; HSIL+, high-grade squamous intraepithelial lesion; SIL, squamous intraepithelial lesion.

[a] Loss to follow-up averaged 3.6% per year in HIV-infected and 3.1% in HIV-uninfected women.

[b] Censoring due to treatment of cervical neoplasia involved 17 HIV-infected women with CD4 cell count <350/μL, 21 with CD4 cell count of 350-499/μL, 35 with CD4 cell count ≥500/μL, and 48 HIV-uninfected women.

[c] Some participants had missing data. An average of 5.5% each year had missing data among HIV-infected women with CD4 cell count <350/μL, 5.7% with CD4 cell count of 350- 499/μL, and 5.3% with CD4 cell count ≥500/μL; and an average of 6.1% of HIV-uninfected women were missing data.

[d] The 95% confidence intervals were calculated using standard life-table methods.

Table 3

Cumulative incidence of any CIN and CIN-2+ in HIV-infected women and HIV-uninfected women who had normal cervical cytology and tested negative for oncogenic HPV DNA at enrollment[a]

Baseline HIV status and CD4 cell count	Year	No. at Start of Interval[b]	No. of Any New CIN	Cumulative Incidence (95% CI)	No. at Start of Interval[c]	No. of New CIN-2+	Cumulative Incidence (95% CI)
HIV-infected CD4 cell count <350 μL	1	44[d]	0	0 (0-0)[e]	44[d]	0	0 (0-0)[e]
	2	42	1	2 (0-7)	42	1	2 (0-7)
	3	40	2	8 (0-15)	40	0	2 (0-7)
	4	34	1	10 (0-19)	34	0	2 (0-7)
	5	32	2	16 (3-27)	33	0	2 (0-7)
CD4 cell count 350-499/μL	1	47	1	2 (0-6)	47	0	0 (0-0)
	2	43	2	7 (0-14)	43	1	2 (0-7)
	3	39	2	12 (2-21)	39	0	2 (0-7)
	4	33	2	17 (5-29)	34	0	2 (0-7)
	5	28	2	23 (9-36)	30	0	2 (0-7)
CD4 cell count ≥500/μL	1	128	5	4 (0-7)	128	1	1 (0-2)
	2	120	4	7 (3-12)	123	1	2 (0-4)
	3	114	4	11 (5-16)	118	2	3 (0-6)
	4	104	4	14 (8-20)	109	2	5 (1-9)
	5	96	3	17 (10-23)	102	1	6 (2-10)
HIV-uninfected	1	145	4	3 (0-5)	145	1	1 (0-2)
	2	138	9	9 (4-14)	141	3	3 (0-6)
	3	123	2	11 (5-16)	132	0	3 (0-6)
	4	115	1	12 (6-17)	126	1	4 (0-7)
	5	105	1	12 (7-18)	116	1	5 (1-8)

[a]The CIN analysis is limited to the four WIHS sites that contributed colposcopic and histologic data (see Methods). Loss to follow-up in these four clinical sites was similar to that among all cytologically normal women in the 2001-2002 cohort (see Table 2). That is, loss to follow-up was 2.9% per year in HIV-infected and 2.9% in HIV-uninfected women.

[b]In the analysis of any new CIN incidence, censoring due to treatment for cervical neoplasia involved 5 HIV-infected woman with CD4 cell count <350/μL, 3 with CD4 cell count of 350-499/μL, 5 with CD4 cell count ≥500/μL, and 9 HIV-uninfected women.

[c]In the analysis of CIN-2+ incidence, censoring due to treatment for cervical neoplasia involved 7 HIV-infected women with CD4 cell count <350/μL, 7 with CD4 cell count of 350-499/μL, 10 with CD4 ≥500/μL, and 10 HIV-uninfected women.

[d]Some participants had missing data. An average of 5.6% each year had missing data among HIV-infected women with CD4 cell count <350/μL, 6.5% with CD4 cell count of 350-499/μL, 4.5% with CD4 cell count ≥500/μL; and an average of 5.6% of HIV-uninfected women were missing data.

[e]The 95% confidence intervals were calculated using standard life-table methods.