Title

Longitudinal assessment of abnormal Papanicolaou test rates among women with HIV.

Journal

AIDS, 34(1)

ISSN

0269-9370

Authors

Massad, Leslie S
Xie, Xianhong
Minkoff, Howard
et al.

Publication Date

2020

DOI

10.1097/qad.0000000000002388

Peer reviewed

HHS Public Access
Author manuscript
AIDS. Author manuscript; available in PMC 2021 January 01.

Published in final edited form as:
AIDS. 2020 January 01; 34(1): 73–80. doi:10.1097/QAD.0000000000002388.

Longitudinal assessment of abnormal Papanicolaou test rates among women with Human Immunodeficiency Virus

L. Stewart MASSAD, M.D.,
Washington University School of Medicine, St. Louis, MO;

Xianhong XIE, Ph.D.,
Albert Einstein College of Medicine, Bronx, NY;

Howard MINKOFF, M.D.,
Maimonides Medical Center, Brooklyn, NY;

Seble KASSAYE, M.D.,
Georgetown University School of Medicine, Washington, DC;

Roksana KARIM, M.D., Ph.D,
University of Southern California, Los Angeles, CA;

Teresa M. DARRAGH, M.D.,
University of California, San Francisco, CA;

Elizabeth T. GOLUB, Ph.D., M.P.H.,
Johns Hopkins University, Baltimore, MD;

Adaora ADIMORA, M.D., M.P.H.,
University of North Carolina, Chapel Hill, NC;

Gina WINGOOD, Sc.D, M.P.H.,
Mailman School of Public Health, Columbia University, New York, New York;

Margaret FISCHL, M.D.,
University of Miami, Miami, FL;

Deborah KONKLE-PARKER, Ph.D.,
University of Mississippi, Jackson, MS;

Howard D. STRICKLER, M.D., M.P.H.
Albert Einstein College of Medicine, Bronx, NY.

Abstract

Objective: To describe longitudinal changes in the prevalence of abnormal Papanicolau testing among women living with HIV

Contact Dr. Massad at: Division of Gynecologic Oncology, Box 8064-37-905, St. Louis, MO 63110. Tel: 314-362-3181. Fax: 314-362-2893. massadl@wustl.edu.

Conflicts of Interest and Source of Funding: Dr. Darragh reports the following financial relationships: Research supplies for anal cytology: Hologic; Advisory Board: BD, Roche; Consultant: TheVax, Antiva, nVision. For the remaining authors none were declared.

Design: Prospective cohort study with sequential enrollment subcohorts

Methods: Four waves of enrollment occurred in the Women's Interagency HIV Study, the U.S. women's HIV cohort (1994–5, 2001–2, 2011–2, 2013–5). Pap testing was done at intake, with colposcopy prescribed for any abnormality. Rates of abnormal Pap test results (atypical squamous cells of uncertain significance or worse) and cervical intraepithelial neoplasia grade 2 (CIN2) or worse were calculated. Logistic regression models assessed changes in prevalence across cohorts after controlling for severity of HIV disease and other risk factors for abnormal Pap tests.

Results: The unadjusted prevalence of any Pap abnormality was 679/1769 (38%) in the original cohort, 195/684 (29%) in the 2001–2 cohort, 46/231 (20%) in the 2011–2 cohort, and 71/449 (16%) in the 2013–5 cohort. In multivariable analysis, compared to risk in the 1994–5 cohort, the adjusted risk in the 2001–2 cohort was 0.79 (95% C.I. 0.59, 1.05), in the 2011–12 cohort was 0.67 (95% C.I. 0.43, 1.04), and in the 2013–5 cohort was 0.41 (95% C.I. 0.27, 0.62) with p for trend < 0.0001.

Conclusion: Rates of abnormal cytology among women with HIV have fallen during the past two decades.

Keywords

Papanicolaou test; human immunodeficiency virus infection in women; Women's Interagency HIV Study

Introduction:

For women, infection with the human immunodeficiency virus-1 (HIV) increases risk for opportunistic infection with genital human papillomaviruses (HPVs), including carcinogenic HPV types [1]. These infections are often manifested morphologically and detected clinically through Papanicolaou testing. Since women with HIV face high cervical cancer risk, it is recommended that they undergo more intensive screening than women without HIV infection. Behavioral factors common among women with HIV, including multiple sexual partners and smoking, also increase their risk for abnormal Pap test results.

Initial studies that defined the relationships among HIV infection, HPV infection, abnormal cytology, and cervical intraepithelial neoplasia (CIN) were published soon after the HIV epidemic in developed countries crossed from homosexual and intravenous drug-using populations into heterosexual populations [1]. However, many of these foundational studies antedate the introduction of combination antiretroviral therapy (cART) more than 20 years ago. Among other profound changes, cART influences the natural history of HPV-related cervical disease. It decreases prevalence and incidence and increases rates of regression of HPV, oncogenic HPV, and cervical squamous lesions [2–6]. This impact is preferentially seen in women with >95% adherence to cART [3]. As high grade cervical lesions have been identified and treated and as women have initiated cART, incident abnormal cytology rates have fallen [7].

Over the past quarter century, cervical cancer incidence in the United States has fallen from 10.5 cases/100,000 women in 1994 to 6.8/100,000 in 2015 [8]. The demographic profile of

HIV infection in the United States also has changed, and the U.S. epidemic increasingly affects minority women in Southern states [9]. How these trends might have impacted the prevalence of abnormal Pap tests among women with HIV is unclear.

The Women's Interagency HIV Study (WIHS) is the U.S. national cohort study of women with HIV. Launched in 1994, the study has included waves of expansion to remain representative of the experience of U.S. women with HIV. The study now incorporates women enrolled prior to introduction of cART as well as during periods with differing guidelines for cART, beginning with targeted cART prescription for women with more severe disease as measured by lower CD4 lymphocyte counts, and more recently expanded to routine cART prescription for all women with HIV. The effectiveness and tolerability of cART has also improved over time.

We set out to assess changes across time in the prevalence of abnormal Pap tests among women recruited to the WIHS and to assess the impact of cART and other risk factors for Pap abnormalities.

Methods

This investigation was part of the WIHS, the ongoing U.S. multicenter prospective cohort investigation of HIV infection and related health conditions among HIV seropositive women and demographically similar seronegative comparison women. The protocols, recruitment processes, procedures, and baseline results of the WIHS have been described [10–12]. Enrollment began prior to the widespread introduction of cART with 2,623 women (2,056 with HIV and 569 without) in 1994–5 at 6 study consortia (Bronx, Brooklyn, Chicago, Los Angeles, San Francisco, and Washington, D.C.). The cohort was expanded by an additional 1141 women (738 with HIV and 403 without) during 2001–2002, when cART was initiated by indication [10]. The WIHS was augmented in 2011–12 by 371 additional women (276 with HIV and 95 without) and most recently by 844 women (610 with HIV and 234 without) in 2013–15. As of late 2016, 1268 women had died, 130 had withdrawn from study, 806 had been discontinued for administrative/funding reasons, 415 had been lost to follow-up, and 2363 were being actively followed.

Local human subjects committees approved study protocols, and written informed consent was obtained from all participants. HIV serostatus was determined by ELISA with confirmatory testing at study entry for all participants and semiannually thereafter for those initially seronegative. Follow up continues.

Pap smears obtained at the intake visit were interpreted centrally according to the 1991 Bethesda system for classification of cervicovaginal cytology. Results were classified as negative for squamous abnormality, atypical squamous cells of undetermined significance (ASCUS), low grade squamous intraepithelial lesion (LSIL), high grade squamous intraepithelial lesion (HSIL), and cancer; women with atypical glandular cells were categorized for analysis with HSIL. Colposcopy was prescribed by protocol for any abnormality, and for this analysis women with any grade of abnormality were considered to have abnormal Pap test results. Cervical biopsies were assessed locally and graded as CIN

1–3, adenocarcinoma in situ (AIS), and cancer. Biopsies reported as CIN2, CIN3, AIS, or cancer were grouped as CIN2+.

In this retrospective analysis of prospectively collected data, we examined all intake Pap test results, along with demographic and behavioral information, cervical biopsy results where available, and cART use. All HIV seropositive WIHS enrollees with baseline results were included. Women were excluded if they had missing Pap test results, prior hysterectomy, or a self-reported cervical cancer history.

HIV RNA level was measured at a certified laboratory. A lower limit of 4000 copies/ml was used as the lower limit, since that was the threshold for detection in the original enrollment cohort.

Comparison between enrollment groups was performed using the following tests: for continuous variables, ANOVA tests or Kruskal-Wallis tests if the variables were not normally distributed; for categorical variables, chi-square tests or Fisher's exact tests if the cell size was small. Logistic regression modelling was used to model the point prevalence of abnormal Pap tests and CIN2+, adjusting for age, race, number of male sexual partners both recent and lifetime, and smoking. The logistic models with and without adjustment of the HIV factors: CD4+ count, HIV viral load, cART use/adherence were studied. P for trends on enrollment period were obtained by treating the variable as ordinal. We elected to assess prevalence rather than progression/regression since prevalence integrates incidence and clearance and some women in later cohorts were enrolled on established cART. A two-sided P-value < 0.05 was considered statistically significant. SAS 9.3 was used for the statistical analysis.

Results:

Of 3677 women enrolled in WIHS, 544 were excluded: 195 had missing Pap test results, while 262 had prior hysterectomy, and 87 self-reported a history of cervical cancer, leaving 3133 women for analysis.

Demographic characteristics of these eligible WIHS enrollees are shown in Table 1, categorized by enrollment dates. In addition to differences in cART use, women in later enrollment cohorts were older and more often African-American. They were less likely to smoke and reported more recent sexual partners. They had higher CD4+ T lymphocyte counts and lower HIV RNA levels.

The prevalence of abnormal Pap test results fell across successive cohorts. Table 2 shows the distribution of Pap test results by grade. The proportion of smears read as ASCUS/LSIL declined across time. In contrast, high grade lesions were stably uncommon, accounting for only 1–3% of all Pap tests throughout the study period. The unadjusted prevalence of any Pap abnormality among women with Pap results was 679/1769 (38%) in the original 1994/5 cohort, 195/684 (29%) in the 2001–2 cohort, 46/231 (20%) in the 2011–2 cohort, and 71/449 (16%) in the 2013–5 cohort.

To avoid misinterpreting as time-related trends differences in the abnormal Pap rates arising from differences in the distribution of cervical cancer risk factors arising from differences in recruitment criteria across the cohorts, we undertook multivariable analyses controlling for recognized cervical cancer risk factors. In one model (Table 3), women in the most recently recruited cohort had less than half the risk for abnormal cytology seen in the initial enrollment cohort. Factors adjusted for in this model that also were associated with abnormal cytology included younger age, lower CD4 count, and higher HIV RNA level. Race, number of recent and lifetime sex partners, smoking history, and reported adherence to cART were not associated with prevalent abnormal cytology in this model. In a different model controlling for age, race, CD4 count, and HIV RNA level, later date at first recorded HIV diagnosis (rather than enrollment date) was associated with lower risk for abnormal cytology: compared to women infected before 1996, the odds ratio for abnormal cytology among those infected 1996–2001 was 0.91 (95% C.I. 0.70, 1.16, p = 0.44), among those infected 2002–7 was 0.89 (95% C.I. 063, 1.25, p = 0.49), among those infected 2008–11 was 0.44 (95% C.I. 0.28, 0.69, p = 0.0004), and among those infected after 2011 was 0.57 (95% C.I. 0.34, 0.98, p = 0.04), with p for trend 0.0004.

In a further model restricted to HIV seronegative women, beyond an initial drop between 1994–95 and 2001–2 we did not find a consistent decline in abnormal cytology across enrollment cohorts: compared to women in the 1994–5 cohort, the odds ratio for abnormal cytology for those in the 2001–2 cohort was 0.65 (95% C.I. 0.44, 0.97, p = 0.03), for those in the 2011–2 cohort 0.79 (95% C.I. 0.32, 1.93, p = 0.60), and for those in the 2013–5 cohort 0.66 (95% C.I. 0.37, 1.17, p = 0.15 and p for trend 0.07).

We also assessed trends in prevalent cervical dysplasia diagnosed in our four cohorts. Table 3 shows the distribution of histologic results across enrollment cohorts. Table 4 shows that after adjusting for known risk factors, CIN2+ prevalence appeared to increase across time (p for trend = 0.07)., with CD4+ remaining the major risk factor. However, by adjusting for cART, CD4+ count, and HIV RNA level, the model in Table 4 essentially separates calendar time (i.e., enrollment date) from the improvements in host immune status that were introduced over time. In another analysis, we found that after excluding cART, CD4+ count, and HIV RNA level there was no significant relation of enrollment date with CIN-2+ (Table 5).

Discussion:

Across the past two decades, risk for abnormal cytology has fallen markedly among women with HIV. This does not appear to reflect a broad secular trend, as we did not find a similar marked decline among HIV-seronegative comparison women enrolled in WIHS. Lower prevalence appears to be due in part to use of cART and associated improvements in immunity as reflected in better CD4 counts and lower HIV RNA levels among more recent recruits to WIHS. However, enrollment cohort remained a significant correlate of declining prevalence of abnormal cytology in multivariable analyses that controlled for these changes. A decline in smoking may have contributed but was not correlated with prevalence in these multivariate models. Healthier recent enrollees were more likely than original WIHS participants to have multiple and recent sexual partners and yet were less likely to have abnormal Pap tests. Our findings deserve confirmation in other large cohorts.

Despite the declining prevalence of abnormal Paps among U.S. women with HIV, they remain at significant risk for abnormal cervical cytology, reflecting their increased risk for opportunistic infection with HPV, for cervical precancer, and for cervical cancer.

We have previously reported that during follow-up within the WIHS, which includes semi-annual cytology screening and treatment of precancer, the rate of Pap abnormalities has declined among [7]. This decline was present for atypical, low grade, and high grade cytology results. These results included both prevalent and incident findings and may have reflected both secular declines in abnormal cytology and the impact of diagnosis and treatment of prevalent cervical lesions. Our current results focus on prevalent findings at enrollment, eliminating study-mediated cervical treatment during follow-up as a cause of a lower rate of abnormal Pap tests. Taken together, falling prevalence and the impact of treatment indicate that the burden of cervical disease on women with HIV has declined substantially over the past two decades.

Interestingly, these decreases in abnormal Pap prevalence over time were detected even after adjustment for CD4 count, HIV RNA level, and cART use in the model. This indicates that these factors did not fully account for the temporal trend. Prior studies in WIHS have shown that other immune cells may also affect the risk of persistent HPV infection in HIV+ women, including levels of plasmacytoid dendritic cells [13], and levels of these cells also improve with use of cART [14]. Thus, immune factors not accounted for in the current study could help explain these trends.

Other potential reasons for declining rates of cervical abnormality among women with HIV are unclear. Among women of similar age in the general population, abnormal Pap test rates recently have been stable to increased [15], and we did not find a comparable strong trend of declining abnormal Pap prevalence in WIHS enrollees without HIV infection. This suggests that our results may be particular to women with HIV. An increase in the diagnostic stringency for reporting ASC-US may have influenced the prevalence of abnormal Pap tests in our study population. While we controlled for recent number of sexual partners, unmeasured changes in sexual behaviors associated with HPV risk may have occurred. Although HPV vaccination has led to declines in HPV16 prevalence among young U.S. women by 2014, our enrollees were generally beyond the age to receive HPV vaccination and unlikely to have been benefitted from off-label HPV vaccination or vaccine-associated herd immunity [16]. More widespread HIV testing may have led to more women being aware of their HIV infections prior to study enrollment and modified sexual risk practices accordingly, reducing abnormal Pap risk. More recently enrolled cohorts also may have had better access to gynecologic care as health care delivery systems for women with HIV have become more comprehensive over the past two decades. WIHS investigators have shown that HPV detection is reduced among women with normal vaginal microbiome profiles [17]. Improvement in the vaginal microbiota in WIHS across time [18] may have contributed to falling rates of abnormal Pap tests.

In contrast to the decline in abnormal cytology prevalence across time in women enrolled in WIHS, we found only a borderline increase in the prevalence of CIN2+ across cohorts after adjusting for CD4+ count, HIV RNA level, and cART use. In any event, even after excluding these variables from the model, the rate of CIN-2+ did not decrease with later WIHS enrollment. This finding is congruent with previous reports from WIHS that lower CD4 counts among women with HIV were associated with only a moderate increase in HPV16 prevalence, the most carcinogenic HPV type, and much greater increases in risk for less oncogenic HPV types. This has suggested that HPV16 is already immunoevasive such that immunosuppression by HIV does not release HPV16 infections from immunosurveillance as much as is seen for other types, and that the corollary is also likely true, namely, that HPV16 prevalence does not decrease as much as other HPV types following immune reconstitution. Thus, it could be anticipated that lower grade lesions would be more greatly impacted by changes in host immune status than CIN-2+. Our finding that time has led to a lower prevalence of abnormal cytology but not CIN2+ suggests that healthier recent WIHS enrollees have less opportunistic, nononcogenic HPV but have persisting high risk for precancerous cervical lesions and continue to merit prompt colposcopy when abnormal cytology is reported, including ASC-US results linked to evidence of carcinogenic HPV infection.

Prior studies using smaller populations have had limited statistical power; for example, the HIV Epidemiologic Research Study concluded that HAART was not associated with progression (P=0.06) or regression (p=0.05) of cytologic abnormality despite hazard ratios suggesting improved outcome) [6]. In addition, WIHS data have shown that controlling for cART adherence and effectiveness, as measured by HIV RNA detection, is important in assessing cART's impact on HPV and cervical disease [3].

This study was limited by several factors. Serial observational cohorts recruited to a research study may not reflect the demographics and the distribution of cervical cancer risk factors in the larger population of U.S. women infected with HIV, and observed changes in abnormal Pap rates may reflect changes among women willing to enroll in research. Additional research is needed to determine whether the decline in abnormal cytology that we have observed can be found in other national cohorts and in the general U.S. population. That said, the WIHS cohort has been shown to be similar in demographic and HIV-related risk behavior to US women with HIV [10, 11] and one of the strengths of this study was its ability to measure how cervical cytology results changed in women infected with HIV based on successive recruitment rounds using standardized enrollment methods and protocols for collection of medical information and cervical screening over time.

Other limitations should be considered in interpreting our results. Pap tests do not always reflect the presence or grade of underlying cervical lesions, but women infected with HIV face logistical and other barriers to colposcopy that may bias analyses of the prevalence of cervical intraepithelial neoplasia. In addition, Pap abnormality rates provide a measure of the burden faced by women with HIV, since all require careful follow-up, given the increased risk for cervical cancer among these immunocompromised women. Finally, we cannot exclude the possibility that the cytopathology community has developed more stringent criteria for the reporting of ASCUS/LSIL across the past two decades.

We cannot speculate on how changes in risk factors for cervical cancer have impacted the clinical burden of abnormal Pap test results for U.S. women with HIV and the clinicians and health systems that care for them, as our cohort enrollments may not fully reflect how the HIV epidemic has changed across time. Multivariable analysis attempted to balance the distribution of cervical cancer risk factors across cohorts, but we cannot exclude the possibility that unidentified differences in our cohorts account for the observed decline in abnormal cytology across time. To minimize the risk for this, we did include in multivariable analysis commonly recognized cervical cancer risks even if they did not appear correlated with Pap abnormality in our enrollees. We did find that host immune status as measured by HIV RNA level and CD4 count continue to have a major impact on rates of abnormal Pap tests. Overall, a more than 50% decline in the prevalence of abnormal cytology among women with HIV, as identified in this large, long-term study, will ease the burden of cervical cancer prevention in this at-risk population. However, stable rates of CIN2+ mean that clinicians caring for these women will still need to maintain networks for referral for colposcopy and dysplasia treatment. More research is also needed to determine whether declining prevalence of abnormal cytology reflects changes in the type distribution of HPV infection; this may assist clinicians and women in deciding whether to be screened with Pap or HPV testing, with the latter test more sensitive but with poor specificity among women with HIV. Further declines in abnormal cytology rates can be expected as young women vaccinated against HPV and presumably protected against cancer enter screening and mature into age cohorts at highest risk for cervical precancer and cancer.

Acknowledgement:

Data in this manuscript were collected by the Women's Interagency HIV Study (WIHS). The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health (NIH). WIHS (Principal Investigators): UAB-MS WIHS (Mirjam-Colette Kempf and Deborah Konkle-Parker), U01-AI-103401; Atlanta WIHS (Ighovwerha Ofotokun and Gina Wingood), U01-AI-103408; Bronx WIHS (Kathryn Anastos and Anjali Sharma), U01-AI-035004; Brooklyn WIHS (Howard Minkoff and Deborah Gustafson), U01-AI-031834; Chicago WIHS (Mardge Cohen and Audrey French), U01-AI-034993; Metropolitan Washington WIHS (Seble Kassaye), U01-AI-034994; Miami WIHS (Margaret Fischl and Lisa Metsch), U01-AI-103397; UNC WIHS (Adaora Adimora), U01-AI-103390; Connie Wofsy Women's HIV Study, Northern California (Ruth Greenblatt, Bradley Aouizerat, and Phyllis Tien), U01-AI-034989; WIHS Data Management and Analysis Center (Stephen Gange and Elizabeth Golub), U01-AI-042590; Southern California WIHS (Joel Milam), U01-HD-032632 (WIHS I - WIHS IV). The WIHS is funded primarily by the National Institute of Allergy and Infectious Diseases (NIAID), with additional co-funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Cancer Institute (NCI), the National Institute on Drug Abuse (NIDA), and the National Institute on Mental Health (NIMH). Targeted supplemental funding for specific projects is also provided by the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Deafness and other Communication Disorders (NIDCD), and the NIH Office of Research on Women's Health. WIHS data collection is also supported by UL1-TR000004 (UCSF CTSA), UL1-TR000454 (Atlanta CTSA), P30-AI-050410 (UNC CFAR), and P30-AI-027767 (UAB CFAR). Additional support for data analysis from R01CA174634 and R01CA230331 (Strickler)

References:

1. Stier E Cervical neoplasia and the HIV-infected patient. Hematol Oncol Clin North Am. 2003;17:873–87. [PubMed: 12852660]
2. Ahdieh-Grant L, Li R, Levine AM, Massad LS, Strickler HD, Minkoff H, et al. Highly active antiretroviral therapy and cervical squamous intraepithelial lesions in human immunodeficiency virus-positive women. J Natl Cancer Inst 2004;96:1070–6. [PubMed: 15265968]

3. Minkoff H, Zhong Y, Burk RD, Palefsky JM, Xue X, Watts DH et al. Influence of adherent and effective antiretroviral therapy use on human papillomavirus infection and squamous intraepithelial lesions in human immunodeficiency virus-positive women. J Infect Dis 2010;201:681–90. [PubMed: 20105077]
4. Menon S, Rossi R, Zdraveska N, Kariisa M, Acharya SD, Vanden Broeck D, et al. Associations between highly active antiretroviral therapy and the presence of HPV, premalignant and malignant cervical lesions in sub-Saharan Africa, a systematic review: current evidence and directions for future research. BMJ Open 2017;7:e015123. doi: 10.1136/bmjopen-2016-015123.
5. Blitz S, Baxter J, Raboud J, Kariisa M, Acharya SD, Vanden Broeck D, et al. Evaluation of HIV and highly active antiretroviral therapy on the natural history of human papillomavirus infection and cervical cytopathologic findings in HIV-positive and high-risk HIV-negative women. J Infect Dis 2013;208:454–62. [PubMed: 23624362]
6. Paramsothy P, Jamieson DJ, Heilig CM, Schuman PC, Klein RS, Shah KV, et al. The effect of highly active antiretroviral therapy on human papillomavirus clearance and cervical cytology. Obstet Gynecol 2009;113:26–31. [PubMed: 19104356]
7. Massad LS, Seaberg EC, Wright RL, Darragh T, Lee YC, Colie C, et al. Squamous cervical lesions in women with human immunodeficiency virus: long-term follow-up. Obstet Gynecol. 2008;111:1388–93. [PubMed: 18515523]
8. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Cervical Cancer. https://seer.cancer.gov/statfacts/html/cervix.html. Accessed January 29, 2019.
9. Lansky A, Brooks JT, DiNenno E, Heffelfinger J, Hall HI, Mermin J. Epidemiology of HIV in the United States. J Acquir Immune Defic Syndr. 2010;55 Suppl 2:S64. [PubMed: 21406989]
10. Barkan SE, Melnick SL, Martin-Preston S, Weber K, Kalish LA, Miotti P, et al. The Women's Interagency HIV Study. Epidemiol 1998;9:117–25.
11. Bacon M, von Wyl V, Alden C, Sharp G, Robison E, Hessol N, et al. The Women's Interagency HIV Study: an observational cohort brings clinical sciences to the bench. Clin Diag Lab Immunol 2005;12:1013.
12. Adimora AA, Catalina Ramirez C, Benning L, Greenblatt RG, Kempf MC, Tien PC, et al. Cohort Profile: The Women's Interagency HIV Study (WIHS). Int J Epidemiol, 2018;47: 393–394i. [PubMed: 29688497]
13. Flagg EW, Torrone EA, Weinstock H. Ecological Association of Human Papillomavirus Vaccination with Cervical Dysplasia Prevalence in the United States, 2007–2014. Am J Public Health. 2016;106:2211–2218. [PubMed: 27736208]
14. Strickler HD, Martinson J, Desai S, Xie X, Burk RD, Anastos K, et al. The relation of plasmacytoid dendritic cells (pDCs) and regulatory T-cells (Tregs) with HPV persistence in HIV-infected and HIV-uninfected women. Viral Immunol. 2014;27:20–5. [PubMed: 24494969]
15. Benlahrech A, Yasmin A, Westrop SJ, Coleman A, Herasimtschuk A, Page E, et al. Dysregulated immunophenotypic attributes of plasmacytoid but not myeloid dendritic cells in HIV-1 infected individuals in the absence of highly active anti-retroviral therapy. Clin Exp Immunol. 2012;170:212–21. [PubMed: 23039892]
16. Flagg EW, Torrone EA, Weinstock H. Ecological association of human papillomavirus vaccination with cervical dysplasia prevalence in the United States, 2007–2014. Am J Public Health 2016;106:2211–8. [PubMed: 27736208]
17. Reimers LL, Mehta SD, Massad LS, Burk RD, Xie X, Ravel J, et al. The Cervicovaginal Microbiota and Its Associations With Human Papillomavirus Detection in HIV-Infected and HIV-Uninfected Women. J Infect Dis. 2016;214:1361–1369. [PubMed: 27521363]
18. Mehta SD, Donovan B, Weber KM, Cohen M, Ravel J, Gajer P, et al. The vaginal microbiota over an 8- to 10-year period in a cohort of HIV-infected and HIV-uninfected women. PLoS One. 2015;10:e0116894. [PubMed: 25675346]

Table 1.

Demographic characteristics of cohorts of women enrolled in the Women's Interagency HIV Study.[1]

Variable	Overall (n = 3328)	Enrollment				P-value
		1994–95 (n = 1868)	2001–02 (n = 713)	2011–12 (n = 243)	2013–15 (n = 504)	
Age, Mean (SD)	36.9 (8.3)	36.0 (7.3)	33.2 (7.1)	42.7 (7.2)	42.8 (9.2)	**<.0001**
Race, n (%)						**<.0001**
White	466 (14)	352 (19)	51 (7)	19 (8)	44 (9)	
Hispanic	760 (23)	459 (25)	227 (32)	36 (15)	38 (8)	
Black	1995 (60)	1006 (54)	401 (56)	176 (72)	412 (82)	
Others	107 (3)	51 (3)	34 (5)	12 (5)	10 (2)	
Smoking, n (%)						**<.0001**
Never	1169 (35)	521 (28)	347 (49)	92 (38)	209 (41)	
Former	505 (15)	309 (17)	95 (13)	35 (14)	66 (13)	
Current	1647 (50)	1031 (55)	271 (38)	116 (48)	229 (45)	
Number of male sexual partners in past 6 mo., n (%)						**<.0001**
0	972 (29)	619 (34)	141 (20)	71 (29)	141 (28)	
1	1803 (55)	958 (52)	452 (64)	136 (56)	257 (51)	
2	292 (9)	147 (8)	72 (10)	21 (9)	52 (10)	
>=3	233 (7)	123 (7)	43 (6)	14 (6)	53 (11)	
CD4+ count, n (%)						**<.0001**
>500	1213 (37)	482 (27)	333 (48)	124 (52)	274 (55)	
200–500	1350 (42)	775 (43)	295 (42)	103 (43)	177 (35)	
<200	675 (21)	543 (30)	71 (10)	12 (5)	49 (10)	
HIV viral load, n (%)						**<.0001**
<=4000	1497 (46)	449 (25)	463 (66)	200 (82)	385 (81)	
4001~20000	597 (18)	420 (23)	118 (17)	24 (10)	35 (7)	
20001~100000	632 (20)	480 (26)	94 (13)	14 (6)	44 (9)	
>100000	515 (16)	474 (26)	24 (3)	5 (2)	12 (3)	
c-ART, n (%)						**<.0001**
No	1785 (54)	1298 (69)	319 (45)	77 (32)	91 (18)	
Yes	1543 (46)	570 (31)	394 (55)	166 (68)	413 (82)	
c-ART, n (%)						**<.0001**
No c-ART	1785 (54)	1298 (69)	319 (45)	77 (32)	91 (18)	
c-ART with Integrase Inhibitor	153 (5)	0 (0)	0 (0)	17 (7)	136 (27)	
c-ART without Integrase Inhibitor	1390 (42)	570 (31)	394 (55)	149 (61)	277 (55)	
Duration of ART before BL in years, median (IQR)	0 (0–1.9)	0 (0–0)	2.0 (0–4.6)	1.2 (0.1–2.9)	3.0 (1.0–5.8)	**<.0001**

[1] Excludes women with prior hysterectomy or a self-reported cervical cancer history and those missing Pap results or information about cART use.

Table 2.

Distribution of Pap test results by grade across WIHS enrollment cohorts. N (row %)

	Cohort				
	1994/95	**2001/02**	**2011/12**	**2013/15**	**Total**
Negative	1090 (62)[1]	489 (71)	185 (80)	378 (84)	2142
ASCUS[2]	368 (21)	118 (17)	28 (12)	33 (7)	547
LSIL[3]	268 (15)	65 (10)	16 (7)	26 (6)	375
HSIL+[4]	43 (2)	12 (2)	2 (1)	12 (3)	69
Total	1769 (56)	684 (22)	231 (7)	449 (14)	3133

[1]Percentages may not add to 100% because of rounding

[2]Atypical squamous cells of undetermined significance

[3]Low grade squamous intraepithelial lesion

[4]High grade squamous intraepithelial lesion, atypical glandular cells, suspicious for malignancy

Table 3.

Multivariable analyses of probability of prevalent abnormal Pap result after adjustment for enrollment CD4 count, enrollment HIV RNA level, and adherence to combination antiretroviral therapy.

a. Full model

Variable		**Odds Ratio**	**95% CI[1]**			**P-value**
			LCL[2]	**UCL[3]**		
Enrollment cohort	1994–95 (ref)	1				**<.0001[4]**
	2001–02	0.79	0.59	1.05		0.11
	2011–12	0.67	0.43	1.04		0.07
	2013–15	0.41	0.27	0.62		**<.0001**
Age (years)	<30 (ref)	1				
	30–34	0.81	0.62	1.06		0.13
	35–39	0.49	0.37	0.66		**<.0001**
	40–44	0.47	0.33	0.65		**<.0001**
	>=45	0.47	0.33	0.67		**<.0001**
Race	White (ref)	1				
	Hispanic	0.99	0.70	1.41		0.97
	Black	1.15	0.84	1.56		0.38
	Others	1.45	0.83	2.54		0.19
Number of male sexual partners in past 6 months	0 (ref)	1				
	1	0.93	0.74	1.17		0.54
	2	1.15	0.80	1.66		0.45
	>=3	0.89	0.60	1.35		0.59
Lifetime number of sex partners	<5 (ref)	1				
	5–9	1.07	0.80	1.44		0.65
	10–49	1.00	0.75	1.32		0.98
	>=50	1.24	0.90	1.70		0.18
Smoking	Never (ref)	1				
	Former	0.98	0.72	1.34		0.89
	Current	1.11	0.88	1.39		0.37
CD4+ count (cells/cmm)	>500 (ref)	1				
	200–500	2.03	1.63	2.53		**<.0001**
	<200	4.87	3.57	6.64		**<.0001**
HIV RNA level (copies/ml)	<=4000 (ref)	1				
	4001~20000	0.95	0.71	1.26		0.71
	20001~100000	1.37	1.03	1.82		**0.03**
	>100000	1.57	1.11	2.21		**0.01**
cART use/adherence[5]	No (ref)	1				
	Yes adherence < 95%	1.57	1.00	2.48		0.052

a. Full model						
Variable		Odds Ratio	95% CI[1]			P-value
			LCL[2]	UCL[3]		
	Yes adherence > 95%	1.35	0.97	1.87		0.07

[1]CI, confidence interval

[2]LCL, lower confidence limit

[3]UCL, upper confidence limit

[4]p-value for trend

[5]cART, combination antiretroviral therapy

Table 4.

Results of cervical biopsies across WIHS enrollment cohorts. N (%)

	1994/5	2001/2	2011/12	2013/15	Total
Normal/benign/no biopsy	1578 (88.9)	623 (91.1)	218 (94.0)	409 (89.1)	2828 (89.8)
CIN1	141 (7.9)	41 (6.0)	10 (4.3)	33 (7.2)	225 (7.1)
CIN2	40 (2.3)	10 (1.5)	3 (1.3)	12 (2.6)	65 (2.1)
CIN3+	17 (1.0)	10 (1.5)	1 (0.4)	5 (1.1)	33 (1.1)
Total	1776 (56.3)	684 (21.7)	232 (7.3)	459 (14.5)	3151 (100.0)

Table 5.

Multivariable analysis of probability of prevalent grade 2 cervical intraepithelial neoplasia or a more severe lesion after adjustment for age, race, sex (recent and lifetime), smoking, CD4+ T cell count, HIV viral load, and cART use/adherence.

Variable		**Odds Ratio**	**95% CI[1]**		**P-value**
			LCL[2]	**UCL[3]**	
Enrollment	1994–95 (ref)	1			0.07[4]
	2001–02	1.47	0.69	3.10	0.32
	2011–12	1.25	0.36	4.32	0.72
	2013–15	2.43	0.96	6.14	0.06
Age	<30 (ref)	1			
	30–34	1.15	0.59	2.23	0.69
	35–39	0.44	0.19	1.03	0.06
	40–44	0.40	0.15	1.06	0.07
	>=45	0.57	0.23	1.39	0.22
Race	White (ref)	1			
	Hispanic	1.02	0.43	2.43	0.97
	Black	0.81	0.38	1.76	0.60
	Others	0.41	0.05	3.36	0.40
# of recent sex partners	0 (ref)	1			
	1	0.71	0.40	1.29	0.26
	2	0.86	0.33	2.25	0.75
	>=3	0.94	0.34	2.57	0.90
Lifetime # of sex partners	<5 (ref)	1			
	5–9	0.98	0.45	2.13	0.96
	10–49	1.14	0.56	2.36	0.72
	>=50	0.80	0.33	1.94	0.62
Smoking	Never (ref)	1			
	Former	1.51	0.67	3.40	0.32
	Current	1.62	0.88	2.98	0.12
CD4+ count	>500 (ref)	1			
	200–500	4.19	2.09	8.39	**<.0001**
	<200	5.27	2.19	12.68	**0.0002**
HIV viral load	<=4000 (ref)	1			
	4001~20000	0.86	0.39	1.92	0.72
	20001~100000	0.87	0.40	1.90	0.72
	>100000	1.27	0.52	3.08	0.60
cART[5] use/adherence	No (ref)	1			
	Yes adherence < 95%	0.80	0.25	2.58	0.70

Variable		Odds Ratio	95% CI[1]		P-value
			LCL[2]	UCL[3]	
	Yes adherence > 95%	1.14	0.50	2.56	0.76

[1] CI, confidence interval

[2] LCL, lower confidence limit

[3] UCL, upper confidence limit

[4] p-value for trend

[5] cART, combination antiretroviral therapy

Table 6.

Multivariable analysis of probability of prevalent grade 2 cervical intraepithelial neoplasia or a more severe lesion after adjustment for age, race, sex (recent and lifetime), smoking.

Variable		Odds Ratio	95% CI[1]		P-value
			LCL[2]	UCL[3]	
Enrollment	1994–95 (ref)	1			0.39[4]
	2001–02	0.90	0.53	1.55	0.71
	2011–12	0.67	0.23	1.93	0.46
	2013–15	1.50	0.81	2.79	0.20
Age	<30 (ref)	1			
	30–34	1.37	0.77	2.42	0.28
	35–39	0.83	0.44	1.57	0.57
	40–44	0.53	0.24	1.20	0.13
	>=45	0.79	0.37	1.69	0.54
Race	White (ref)	1			
	Hispanic	1.10	0.56	2.14	0.78
	Black	0.77	0.42	1.41	0.39
	Others	0.92	0.26	3.29	0.90
# of recent sex partners	0 (ref)	1			
	1	0.94	0.58	1.52	0.81
	2	0.82	0.34	1.94	0.65
	>=3	1.03	0.42	2.53	0.94
# of lifetime sex partners	<5 (ref)	1			
	5–9	0.89	0.49	1.64	0.71
	10–49	0.79	0.44	1.41	0.42
	>=50	0.58	0.29	1.16	0.12
Smoking	Never (ref)	1			
	Former	1.15	0.56	2.34	0.70
	Current	1.81	1.10	2.98	**0.02**

[1] CI, confidence interval

[2] LCL, lower confidence limit

[3] UCL, upper confidence limit

[4] p-value for trend