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Results of the Women's Self-Performed Anal Pap Trial in Human Immunodeficiency Virus–Infected Women

Candice J. McNeil, MD, MPH^{*}, Christina S. Kong, MD[†], Andrew Anglemyer, PhD[‡], Vivian Levy, MD[§], and Yvonne Maldonado, MD[¶]

^{*}Section on Infectious Diseases, Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC

[†]Department of Pathology, Stanford University, Stanford

[‡]Collaborative Health and Human Services, California State University, Monterey Bay

[§]San Mateo County Health System, Section of Infectious Diseases and Stanford University, Division of Infectious Diseases and Geographic Medicine

[¶]Division of Pediatric Infectious Diseases, Department of Pediatrics, Stanford University, Stanford, CA

Abstract

High-risk human papillomavirus anal infections are common in human immunodeficiency virus–infected women. We conducted a crossover study in 30 women seen in a California human immunodeficiency virus clinic, to test the feasibility of self-performed anal Pap smears. Women found the tests acceptable and feasible. Compared with physician-collected specimens, results were highly concordant for anal cytology ($\kappa = 0.53$) and high-risk human papillomavirus typing ($\kappa = 0.59$ inclusive of equivocal results, or $\kappa = 0.81$ excluding equivocal results).

Keywords

HIV; women; self-performed; anal Pap smear; HPV

Persistent high-risk human papillomavirus (HR-HPV) infection is common in both anal and cervical cancers. Cases of anal cancer have increased nearly 2-fold between 1975 and 2009.¹ In a recent study of 171 women infected with human immunodeficiency virus (HIV) who were taking combination antiretroviral therapy, 29% of women had an abnormal anal Pap smear. Among these women, 19% had atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesions; 10% had ASCUS and high-grade squamous intraepithelial lesions could not be excluded; and 0.6% had anal carcinoma.² These results support the importance of surveillance to understand and prevent HPV-associated genital diseases in this population. Although some guidelines advocate anal Pap

Correspondence: Candice J. McNeil, MD, Section on Infectious Diseases, Department of Internal Medicine, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157. cmcneil@wakehealth.edu.

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screening in HIV-infected persons with a history of genital warts or in women with a history of receptive anal intercourse or abnormal cervical Pap smears,³ implementation of regular anal Pap tests has been limited by a lack of randomized controlled trials to test whether early diagnosis and treatment of anal intraepithelial neoplasia would decrease rates of anal cancer.

Most studies of self-collected anal Pap smears have been reported in men who have sex with men. In these cohorts, self-collected anal Pap smears were considered a useful screening tool for anal cancer, with a high degree of user acceptability and good concordance between self-performed and provider-performed specimens.⁴ Similarly, self-performed rectal specimens were considered acceptable and useful for sexually transmitted infection (STI) screening in men and women.⁵

There is a paucity of data on self-collected anal Pap smears in HIV-infected women. Thus, we performed this pilot study to explore acceptability and feasibility of a self-performed anal Pap test in HIV-infected women and evaluate the concordance of cytology and HPV typing in self-collected versus physician-collected anal Pap smears.

Fifty-eight women were screened and 30 women enrolled from 2 county HIV clinics in northern California between January 2012 and April 2013. All women were taking combination antiretroviral treatment, aside from one who was an elite controller. Subjects were eligible for participation if they were 18 years or older; able to independently give consent in English or Spanish; and HIV-infected with no history of anal Pap smears, anogenital surgery within the last 6 months, or health conditions that could limit their ability to complete study procedures. Demographics, health history, health behaviors, and baseline HPV knowledge surveys were completed before study Pap procedures. Written consent was obtained from participants before study enrollment. This study was approved by the San Mateo Medical Center and Stanford University Institutional Review Boards.

Participants were randomized to conduct a self-performed anal Pap test, either before or after a physician visit for anal and cervical Pap procedures. After the Pap procedures, participants received a brief questionnaire assessing the acceptability of self-performed testing. Self-reported HIV status, medical history, health care maintenance, and social histories were confirmed by chart review. Women with abnormal (results other than negative for intraepithelial neoplasm) cervical and/or anal Pap study findings were contacted and referred for follow-up medical care.

Participant specimen collection kits included a pair of gloves, 2 sterile Dacron swabs, a marked disposable measure indicating the depth of swab insertion, a sealed vial of ThinPrep cytology solution (Hologic Inc, Bedford, MA), and an illustrated instruction sheet. Patient-performed and physician-performed anal Pap specimens were obtained with a moist Dacron swab agitated in ThinPrep preservative. Physician-performed cervical Pap smears used a cytobrush rinsed in ThinPrep, according to the manufacturer's recommendations.

Specimens were processed immediately or refrigerated in a research laboratory and batched for specimen processing at the Stanford Hospital & Clinics Cytopathology and Virology Laboratories. Both laboratories were blinded to the participants' HIV and HPV statuses. Cytology specimens were considered adequate if at least 5000 squamous cells were present.

Cervical and anal specimens were initially screened by the ThinPrep Imaging system (Cytoc, Boxborough, MA) then reviewed by a cytotechnologist. Any abnormal results were verified by a cytopathologist. Results were interpreted and reported using the 2001 Bethesda system guidelines.⁶ The remainder of the ThinPrep fluid sample was transported to the Stanford Hospital & Clinics Virology Laboratory. Specimens were processed using the *Digene* HC2 HPV DNA test (Qiagen), which detects 13 high-risk HPV types (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68). Results were reported as positive, negative (<1.0 pg/mL), or equivocal (low positive results near the 1.0 pg/mL cutoff).

Statistical analyses were performed with the R software package.⁷ Basic descriptive statistics were used to describe participant characteristics. Kappa statistics were calculated for specimens where there was available information on both physician-obtained and participant-obtained anal Pap collections.

Demographic characteristics are summarized in Table 1. Mean CD4 count ($P = 0.59$) and years since HIV diagnosis ($P = 0.1$) were not significantly associated with history of abnormal anal cytology. The mean nadir CD4 for patients with history of ever having an abnormal anal Pap result was significantly different (159.4 cells/mm³) than the mean nadir CD4 for patients without such a history (369.5 cells/mm³) ($P = 0.001$). Half of enrolled women reported a history of abnormal cervical Pap smears, most of which were ASCUS (53%). Sixty percent of participants had a history of STIs, most of which were genital herpes ($n = 11$). History of STIs was not associated with history of abnormal cervical Pap smears ($P = 0.97$). Eighteen participants reported sexual activity in the last year; most (60%) reported a single partner with whom they engaged in vaginal and oral sex. The most common self-reported risk behavior for STIs was inconsistent condom use (43%). Half of the participants reported ever smoking. Most participants reported the use of preventive screening measures, such as cervical Pap smears and age-appropriate mammogram screening (Table 1).

Participant-performed anal Pap, physician-performed anal Pap, and physician-performed cervical Pap specimens were collected from all participants. A high percentage of physician-performed and participant-performed anal Pap specimens was satisfactory for evaluation (Table 2). The proportion of anal Pap results that were abnormal was 32%. There was moderate agreement between participant-collected and physician-collected specimens for anal cytology ($\kappa = 0.53$). The agreement between participant-performed and physician-performed anal specimens for HR-HPV was moderate or very good, depending on the inclusion or exclusion of equivocal tests ($\kappa = 0.59$ and $\kappa = 0.81$, respectively). Overall, anal and cervical cytology results were uncorrelated (correlation coefficient = -0.05 , $P = 0.78$). Similarly, anal and cervical HR-HPV cytology results were also uncorrelated (correlation coefficient = 0.12 , $P = 0.80$).

Ninety-seven percent of participants responded they would be agreeable to a future anal Pap test if recommended by their physician. Seventy percent indicated that the self-administered anal Pap test was easy to perform, and 96% found the illustrated instruction sheet useful. Variables, such as the order in which specimens were collected and the language of the participant, did not affect participants' opinions about ease of the self-administered test or who they preferred to perform the procedure. Participants showed no clear preference for

who performed the anal Pap procedure (self-performed [n = 9], physician performed, [n = 11], and no preference, [n = 10]). Furthermore, for both the clinician-performed and participant-performed tests, the order in which the samples were taken was not significantly related with positive test results (Fisher exact test, $P = 0.64$ and $P = 0.28$, respectively). Similarly, the order also had no relationship to HR-HPV results from physician-performed or participant-performed tests (Fisher exact test, $P = 0.49$ and $P = 0.34$, respectively).

Anal Pap self-collection to screen for abnormal anal cytology and anal HPV infection was an acceptable and feasible screening approach in HIV-infected women in this pilot study. Although 34% of specimens were inadequate for evaluation in a previous study of anal Pap tests in HIV-infected women,⁸ adequacy in our study was similar to that reported in a group of mostly HIV-negative men who have sex with men. In addition, fewer inadequate specimens were noted with provider-performed anal specimen collection.⁹ One study of self-obtained anal Pap tests in 46 HIV-infected participants (8 women) found reasonable concordance between participant-performed and physician-performed specimens, and acknowledged that limited exposure or experience among their participants may have contributed to lower rates than reported in the literature.¹⁰ We found higher than expected agreement between participant-collected and physician-collected specimens for anal cytology and moderate or very good agreement for HR-HPV. The prevalence of abnormal anal Pap results in our study was similar to that reported by others.²

In a previous study of 100 HIV-negative high-risk Puerto Rican women ages 18 to 34 years, concerns about the ability to correctly perform self-collection influenced the preferred method of specimen collection. Similar findings were noted in cervicovaginal self-collection studies.¹¹ However, participants in our study did not express concerns about proper collection techniques. Most participants with abnormal anal cytology had a previous history of abnormal cervical cytology. Because women with a history of cervical intraepithelial neoplasia are at higher risk for HR-HPV infection and anal cancer, this finding was expected.¹² Goodman et al.¹³ also noted the high likelihood of genotypic concordance, that is, that HPV infection at 1 site may serve as a reservoir for the other. In our study, anal and cervical cytology results and HR-HPV results were uncorrelated. This may be due to the limited number of participants. Similarly, we had limited ability to stratify cytological findings and risk behaviors by CD4 count. Nonetheless, we observed that the mean CD4 nadir (but not years from HIV diagnosis) was significantly different between participants with and without a history of abnormal anal cytology, which has previously been reported.¹⁴

A few participants in our study had equivocal HPV test results, which were low positive results near the 1.0 pg/mL cutoff measurement for HPV DNA results obtained with Digene HC2 techniques. In this range of results, signal leak and cross-reactivity with low-risk HPV types may cause false-positive findings.¹⁵

Given the high level of concordance for cytology and HPV typing for anal Pap smears obtained by self-collected or physician-collected techniques, we conclude that self-collected anal Pap tests have strong potential for utility in screening HIV-infected women. However, a larger study to confirm this conclusion is needed.

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TABLE 1**Demographics, Health History, and Behavioral Practices of Study Participants**

Demographics	All Women (N = 30)
Mean age (SD)	48 (10)
Race/ethnicity (%)	
Non-Hispanic black	14 (47)
Hispanic	8 (27)
Asian/Pacific Islander	4 (13)
Non-Hispanic white	3 (10)
Multiracial/other	1 (3)
Education (%)	
High school	16 (53)
College	8 (27)
Graduate	2 (7)
Not indicated	3 (10)
Other	1 (3)
Marital status (%)	
Single	19 (63)
Married, living with spouse	5 (17)
Married, not living with spouse	2 (7)
Partnered	1 (3)
Not indicated	1 (3)
Health history	
Mean number of pregnancies (SD)	3 (2)
Mean CD4 count (SD), cells/mm ³	581 (324)
Mean CD4 nadir (SD), cells/mm ³	304 (279)
History of cancer (%)	2 (7)
STI history (%)	18 (60)
Sexual/behavioral practices	
Mean sexual partners, 2 mo	1
Mean sexual partners, 12 mo	1
Ever smoker (%)	16 (53)
Inconsistent condom use (%)	13 (43)
History of injection drug use or noninjectable drugs (%)	11 (37)
Needle sharing (%)	9 (30)
Commercial sex work (%)	7 (23)
History of heavy alcohol use (%)	5 (17)
Health maintenance/screening history (%)	
Cervical Pap screening in lifetime	24 (80)
History of abnormal cervical Pap in lifetime	15 (50)
Age > 40 years (n = 23) and mammogram	19 (83)
Age >50 years (n = 15) and colonoscopy	4 (27)

TABLE 2

Self-Performed Versus Physician-Performed Anal Pap Tests in Women: Cytology and High-Risk HPV Identification

	Physician-Performed Anal Pap (%)	Participant-Performed Anal Pap (%)	Physician-Performed Cervical Pap (%)
Pap satisfactory [*] for evaluation	N = 28 (93)	N = 26 (87)	N = 30 (100)
Negative for intraepithelial lesion or malignancy	19 (68)	21 (81)	24 (80)
LSIL [†]	3 (11)	2 (8)	4 (13)
ASCUS	6 (21)	3 (11)	2 (7)
Satisfactory [‡] for evaluation	N = 30 (100) [‡]	N = 27 (90) [‡]	N = 30 (100)
HR-HPV negative	15 (50)	18 (67)	20 (66)
HR-HPV positive	12 (40) [§]	8 (30) [§]	8 (27)
HR-HPV equivocal	3 (10) [¶]	1 (4) [¶]	2 (7)

HR-HPV (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56 58, 59, 68).

^{*} Cytology specimens were considered adequate if at least 5000 squamous cells were present and inadequate if fewer squamous cells were present.

[†] Includes some results described as LSIL-H or low-grade squamous intraepithelial lesion, cannot exclude high-grade squamous intraepithelial lesion.

[‡] $\kappa = 0.53$ indicates moderate agreement between physician- and participant-performed anal cytology specimen adequacy.

[§] $\kappa = 0.81$ indicates very good agreement between physician- and participant- performed HR-HPV positivity, excludes equivocal results.

[¶] $\kappa = 0.59$ indicates moderate agreement between physician- and participant-performed HR-HPV positivity, includes equivocal results.

LSIL, low-grade squamous intraepithelial lesion.