Published in final edited form as:

AIDS. 2014 July 17; 28(11): 1696–1698. doi:10.1097/QAD.0000000000000285.

Cervical HPV Testing to Triage Borderline Abnormal Pap Tests in HIV Co-Infected Women

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Clinical guidelines for women in the general population with a Pap test read as atypical squamous cells of undetermined significance (ASC-US) recommend reflex testing for oncogenic human papillomavirus (oncHPV) infection. Those who test positive for oncHPV are triaged to colposcopy while those who are oncHPV-negative have repeat testing in three years.[1]

In women with HIV infection, however, there are currently conflicting clinical recommendations regarding the follow-up of an ASC-US Pap test. The United States Public Health Service guidelines recommend that HIV-seropositive women with ASC-US have immediate colposcopy or a repeat Pap test 6–12 months later, whereas the American Society for Colposcopy and Cervical Pathology guidelines allow for oncHPV reflex triage, as in the general population. To date, one small study of oncHPV testing for triage of ASC-US among HIV-infected women found 100% sensitivity and 70% specificity, but involved only 5 cases of pre-cancer (i.e., cervical intraepithelial neoplasia grade 2 or worse; CIN-2+) and 35 controls.[2] A second study found much lower sensitivity, but tested only cervicovaginal lavage specimens, not cervical swabs used in clinical practice.[3]

OncHPV DNA testing was conducted in convenience specimens (i.e., cervical swabs initially collected for HIV RNA testing) obtained at the time of the first ASC-US Pap detected during semi-annual follow-up between 2000–2008 in a cohort of HIV-seropositive women. Each specimen had been used in prior PCR testing. Overall, 140 women with ASC-US and available swabs were evaluated, including all 24 CIN2+ cases and a random sample of 116 controls (30 CIN-1 and 86 normal) in the WIHS cohort. Swabs were tested for oncHPV using a well-established HPV DNA PCR assay.[4, 5] OncHPV types included HPV

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16/18/31/33/35/39/45/51/52/56/ 58/59/68, with specimen adequacy determined by amplification of the human beta-globin gene. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were determined using a logistic regression model incorporating inverse sampling fractions as weights,[6] to account for the sampling strategy, as well as specimen unavailability or inadequacy.[6]

Characteristics of CIN-2+ cases and controls at the time of their ASC-US diagnosis were similar (supplemental table 1). Patients with CIN2+ did not differ significantly from controls in terms of demographics, current CD4 cell count, current tobacco use, and current of lifetime sexual behaviors. Table 1 shows the HPV DNA test results by case-control status. OncoHPV detection was more common in CIN-2+ cases (16/17; 94%) than controls (35/97; 36%; $p<0.001$). This included oncoHPV in 4 of 4 (100%) cases of CIN-3+, 3 of 3 (100%) CIN-2/3, and 8 of 9 (92%) CIN-2. While amplification was not obtained in 19% of the convenience specimens tested, the oncoHPV rate in cases shows that under-detection of oncoHPV was not a problem among women with adequate specimens.

Overall, sensitivity was 94% (95% CI: 68% –99%) and specificity was 64% (95% CI: 54% – 73%) for CIN2+ (Table 1). The weighted PPV was 23% (95% CI: 14% – 34%) and the weighted NPV was 99% (95% CI: 93% – 100%).

The current study provides evidence that oncoHPV reflex testing is potentially useful in the triage of ASC-US among HIV-seropositive women. The high sensitivity and moderate observed specificity of oncoHPV reflex testing indicate that few cases of CIN2+ would be missed, and unnecessary colposcopy would be avoided in approximately two-thirds of HIV-seropositive women with ASC-US who do not have CIN-2+. The chief limitations of the current investigation were moderate size and the non-amplification of a subset of the convenience specimens used in this study. Additional larger and more comprehensive studies are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by R01 CA85178 and R01 CA174634 from NCI (PI H Strickler). 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 (Michael Saag), U01-AI-103401; Atlanta WIHS (Ighovwerha Ofotokun and Gina Wingood), U01-AI-103408; Bronx WIHS (Kathryn Anastos), U01-AI-035004; Brooklyn WIHS (Howard Minkoff and Deborah Gustafson), U01-AI-031834; Chicago WIHS (Mardge Cohen), U01-AI-034993; Metropolitan Washington WIHS (Mary Young), 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 (Alexandra Levine and Marek Nowicki), 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. WHS data collection is also supported by UL1-TR000004 (UCSF CTSA) and UL1-TR000454 (Atlanta CTSA).

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Table 1

Oncogenic HPV DNA detection in cervical swabs from 140 HIV co-infected women with ASC-US Pap test results, according to their colposcopic / histologic findings

Results of Colposcopy & Histology	Oncogenic HPV DNA			Percent (%) HPV+
	Yes	No	Inadequate *	
< CIN-2	35	62	19	36%
CIN-2+	16	1	7	94%
<i>Sensitivity</i>	94%			
<i>Specificity</i>	64%			

* The PCR assay did not amplify in 16% with <CIN-2 and 24% with CIN-2+.