

# Higher Prevalence of Human Papillomavirus-Related Cervical Precancerous Abnormalities in HIV-Infected Compared to HIV-Uninfected Women

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**Introduction:** Persistent high risk human papillomavirus (hrHPV) has been associated with cervical abnormalities and cancer. There are few studies comparing HIV-infected with uninfected African American women from the Southern U.S. We evaluated medical records of a women's cohort in an urban clinic in Tennessee to assess the prevalence of hrHPV and cytology correlates, as well as HPV vaccination rates.

**Methods:** We reviewed medical records of 50 HIV infected and 304 HIV uninfected women, including Pap smears and hrHPV.

**Results:** HIV-infected women were older than HIV-uninfected women ( $p < 0.0001$ ) and were more likely to have hrHPV ( $p < 0.0001$ ) and LGSIL/HGSIL ( $p = 0.006$ ). Within the HIV uninfected group, Hispanic women were younger than non-Hispanic African American women ( $p = 0.04$ ) and non-Hispanic white women ( $p = 0.0002$ ). Non-Hispanic African-American women were younger ( $p = 0.004$ ) than non-Hispanic white women. Both HIV-uninfected and HIV-infected women had an 11-fold and 5-fold odds, respectively, of having precancerous lesions when harboring hrHPV, compared to hrHPV-uninfected women. Of the 125 HIV-uninfected women, only 17% had received at least one dose of the HPV vaccine. None of the 21 vaccine recipients had evidence of SILs compared to 9% of vaccine non-recipients ( $p = 0.35$ , Fisher's exact test).

**Conclusion:** HIV-infected women remained at significantly higher risk for developing cervical precancerous lesions when exposed to hrHPV than their uninfected counterparts. Hispanic women were least likely to have been vaccinated. Missed HPV vaccination trended towards being associated with a higher odds of precancerous lesions. Routine HPV vaccination should be reinforced for adolescents and young women using public hospital facilities of all races and ethnic backgrounds.

**Keywords:** HPV ■ HIV ■ cervix ■ screening ■ southern US ■ health disparities ■ HPV vaccine ■ Race/ethnicity

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## INTRODUCTION

Cervical cancer is the second most common cancer in women worldwide.<sup>1-3</sup> Human papillomavirus (HPV) accounts for the vast preponderance of

invasive cervical cancers (ICC).<sup>4</sup> Of >140 HPV types identified,<sup>5</sup> about 30-40 are anogenital types,<sup>5,6</sup> while 15-20 are oncogenic.<sup>16,18,31,33,35,39,45,51,52,56,58,59,68</sup> A majority of ICC worldwide are caused by HPV 16 (54%) and HPV 18 (13%), though data from low and middle income countries are scarce when compared to high income nations.<sup>7</sup> Precancerous lesions such as, cervical intraepithelial neoplasia (CIN) grade 2 and 3 lesions and adenocarcinoma in situ are markers of those women at highest risk for the development of ICC.

In the United States, conspicuous health disparities exist in the prevalence of ICC among racial/ethnic groups.<sup>8</sup> The reported incidence rates are significantly higher in African American (odds ratio [OR] 1.34) and Hispanic (OR 1.55) women compared to white women.<sup>9</sup> ICC incidence among HIV-infected females in the US is over three times higher among HIV-infected compared to uninfected women (16 vs. 5 per 100,000 person-years).<sup>10</sup>

Studies have described HPV prevalence and types in HIV-infected women,<sup>11</sup> and have compared these parameters to HIV-uninfected U.S. women.<sup>12-17</sup>

While race/ethnicity and immunodeficiency may affect rates of HPV infection, persistent high risk HPV (hrHPV) has been consistently and strongly associated with cervical intraepithelial neoplasia (CIN).<sup>18,19</sup> Given a dearth of such data from the American South, we evaluated the association of HPV infection on cervical abnormalities in African-American and women of other ethnic/racial backgrounds in public sector urban clinics in Nashville, Tennessee.

## METHODS

We reviewed electronic medical records in a cohort of 50 HIV-infected and 304 HIV-uninfected women after obtaining approval from Institutional Review Board of Meharry Medical College. All women had attended

**Table 1.** High-risk human papillomavirus (hr-HPV) infection in HIV-infected and HIV-uninfected women in a public hospital in Nashville, Tennessee, 2012–2015

|                                                 | HIV Infected (n=50) | HIV Uninfected (n=304) | P        |
|-------------------------------------------------|---------------------|------------------------|----------|
| Age in years, Mean ( $\pm$ SD)                  | 47 ( $\pm$ 11)      | 32 ( $\pm$ 11)         | <0.0001* |
| Proportion with hr-HPV (%)                      | 19/50 (38)          | 39/304 (13)            | <0.0001# |
| Proportion with LGSIL/HGSIL (%)                 | 8/50 (16)           | 14/304 (5)             | 0.006#   |
| Proportion with LGSIL/HGSIL/ASCUS/Dysplasia (%) | 15/50 (30)          | 37/304 (12)            | 0.003#   |

\*Two-tailed t-test

#Two-tailed Fisher's Exact test

Meharry's Community Wellness and Obstetrics/Gynecology out-patient clinics. Data included patient demographics (age, race/ethnicity), HIV status, HPV vaccination status, Pap test results, and colposcopy results. From records of HIV-infected women, we abstracted their CD4+ cell count and viral load data. Using cervical cytology (Papanicolaou [Pap] test), we used the 2001 Bethesda classification: atypical squamous cell of undetermined significance (ASCUS), low and high grade squamous intraepithelial lesions (LGSIL/HGSIL), and atypical glandular cells. We defined "abnormal cytology" in women only when they had either LGSIL or HGSIL. The screening Pap test used was a liquid based SurePath<sup>TM</sup> test (an image guided system) performed at Lab Corp (Birmingham, AL).

To detect hrHPV, we used Hybrid Capture<sup>®</sup> 2 High-Risk HPV DNA Test<sup>TM</sup> (Digene Corporation, Gaithersburg, MD, USA) technology that detects 13 high-risk HPV types using full genome probes. Any identified oncogenic serotype was considered hrHPV.<sup>16,18,31,33,35,39,45,51,52,56,58,59,68</sup>

## RESULTS

**HIV-infected women:** Forty-six women were non-Hispanic African American, four were non-Hispanic white, and none was Hispanic. HIV-infected women (mean age 47 years) were older than HIV-uninfected women (mean age

32 years,  $p < 0.0001$ ). HIV-infected women were more likely to have hrHPV ( $p = < 0.0001$ ) and abnormal cytology (LGSIL/HGSIL) ( $p = 0.006$ ) than HIV-uninfected women (see [Table 1](#)). All eight HIV-infected women with LGSIL/HGSIL (100%) had hrHPV, while 11 of 42 HIV-infected women without LGSIL/HGSIL (26%) were hrHPV positive ( $p = < 0.0001$ , 2-tailed Fisher's exact test). CD4+ cell counts were lower in women with abnormal cytology and hrHPV than those without one or both of these parameters, but this was not statistically significant with our sample sizes (see [Table 2](#)). All women were receiving combination antiretroviral therapy (ART), but we did not have data as to their adherence.

**HIV-uninfected women:** Hispanic women ( $n = 27$ ) were younger (mean age 28 years) than the non-Hispanic African

Americans ( $n = 200$ ; mean age 32 years;  $p = 0.04$ ) and non-Hispanic whites ( $n = 45$ ; mean age 37 years;  $p = 0.0002$ ). Non-Hispanic African American women were also younger than non-Hispanic white women ( $p = 0.004$ ) (see [Table 3](#)). (Race/ethnicity was either "other" or was unknown in 32 women.) Among these HIV-uninfected women, 8 of 39 (21%) women with hrHPV had abnormal cytology (LGSIL/HGSIL) compared with 6 of 265 (2.3%) women who were hrHPV negative ( $p = < 0.0001$ ) (see [Table 4](#)).

**Table 2.** Immunologic, virologic and cytologic parameters by hrHPV Status in 50 HIV-infected Women

|                                       | hrHPV (n=19)             | No hrHPV (n=31)           | P        |
|---------------------------------------|--------------------------|---------------------------|----------|
| CD4+ cells/ $\mu$ L Mean ( $\pm$ SD)  | 519 ( $\pm$ 330)         | 632 ( $\pm$ 304)          | 0.22*    |
| Viral load copies/mL Mean ( $\pm$ SD) | 1099.79 ( $\pm$ 4706.22) | 5570.58 ( $\pm$ 16837.58) | 0.26*    |
| Proportion LGSIL/HGSIL (%)            | 8/19 (16)                | 0/31 (0)                  | <0.0001# |

\*Two-tailed t-test

#Two-tailed Fisher's Exact test

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