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Original article

Hybrid capture as a tool for cervical lesions screening in HIV-infected women: insights from a Brazilian cohort

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ABSTRACT

Introduction: Cervical cancer remains an important burden for HIV-infected women in the era of combination antiretroviral therapy. Recommendations for cervical screening in these women diverge and may include high-risk HPV (HRHPV) testing. We aimed to evaluate the clinical usefulness of a single HRHPV testing for cervical screening of HIV-infected women.
Methods: 723 HIV-infected women from a Brazilian prospective cohort were included between 1996 and 2012. Inclusion criteria were: normal cervical cytology at baseline and having a HRHPV-test at baseline. We calculated incidence rates of any squamous intraepithelial lesion (SIL) and high grade SIL+ (HSIL+) and negative predictive values (NPV) within 12 and 36 months. Hazard Ratios were obtained using Cox proportional hazards regression models.
Results: Incidence rate for both outcomes was low (9.9 cases per 100 PY [95% CI 8.8–11.0] for any SIL and 1.3 cases per 100 PY [95% IC 0.9–1.8] for HSIL+). Women with a HRHPV positive status at baseline had 1.7-fold (95% CI 1.3–2.2) and 3.2-fold (95% CI 1.5–7.1) increased risk of presenting any SIL and HSIL+, respectively, during follow-up. Negative-HRHPV test presented high NPV for both periods and outcomes (any SIL: 92.4% [95% CI 89.7–94.6] for 12 months and 80.9% [95% CI 77.2–84.3] for 36 months; and HSIL+: 99.8% [95% CI 98.9–100.0] for 12 months and 99.0 [95% CI 97.6–99.7] for 36 months).
Conclusions: Incidence of any and high grade cytological abnormality was significantly higher among HIV-infected women with positive-HRHPV test. A single negative-HRHPV test helped reassure follow-up free of cytological abnormalities through three years of follow-up in HIV-infected women with negative cytology.

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Introduction

Cervical cancer remains an important disease burden for HIV-infected women in the era of combination antiretroviral therapy (cART). These women bear an increased human papillomavirus (HPV) prevalence and reduced clearance due to immune impairment, leading to reactivation of latent HPV infections and induced HPV-related lesions.[1–5] This association is more pronounced in the context of advanced immunodeficiency[6–10] with a low cumulative incidence of intraepithelial lesions among HIV-infected women with CD4+ counts above 500 cells/mm^3 and HPV-negative at baseline.[2] A systematic review found a slightly higher risk for cervical cancer after the introduction of combined antiretroviral therapy (cART).[11] The increased survival associated with cART use has been linked to a higher risk of cancer, including those linked to HPV.[11,12]

Recommendations for cervical screening in HIV-infected women diverge. The Centers for Disease Control and Prevention (CDC) recommendations include semiannual cervical screening with cytology in the first year after HIV diagnosis, followed by annual cytology.[13] On the other hand, the World Health Organization recently recommended a three-year interval for HIV-infected women whose screening was negative.[14] The American Society of Colposcopy and Cervical Pathology suggests similar management of abnormal cytology for HIV-infected and uninfected women, which includes the use of high-risk HPV (HRHPV) testing.[15] Brazilian guidelines recommend cytology screening every 3 years after two negative annual results for HIV-uninfected women with ages 25–64 years, and annual screening for HIV-infected women with CD4+ count higher than 500 cells/μL and every 6-months for lower counts.[16] Although the American College of Obstetricians and Gynecologists have recommended high-risk HPV (HRHPV) cervical screening testing as a complement for cytology in HIV-infected women,[17] this test is not included in the Brazilian cervical cancer screening recommendations for this population.[16]

HRHPV testing has been employed as a useful tool for cervical screening in HIV-uninfected women, but data on its role for the management of HIV-infected women is limited, especially in low and middle income settings. Data regarding this topic in Latin America are lacking. An economic analysis suggested that combining both cytology and HRHPV testing might be cost-effective for HIV-infected women in Brazil.[18] In this manuscript, our aim was to evaluate the clinical usefulness of a single HRHPV as a screening test for cervical abnormalities among HIV-infected women in a Brazilian cohort.

Methods

Ethic statement

The study was reviewed and approved by the Evandro Chagas National Institute of Infectious Diseases ethics review board, at Oswaldo Cruz Foundation. All information was de-identified prior to analysis. All women signed an informed consent form prior to study procedures.

Study population

The Evandro Chagas National Institute of Infectious Diseases HIV-Infected Women's Cohort is a prospective open cohort, established in May 1996 in Rio de Janeiro, Brazil. Cohort procedures have been published previously.[19] Briefly, after signing the informed consent form, data were obtained through structured questionnaires and samples were collected for cervical cytology, HPV and sexually transmitted diseases (STD) testing. All women underwent a pelvic exam at baseline and subsequent study visits (semi-annually or annually), with collection of endocervical samples for HPV testing and conventional cytology. Cervical cytology, performed with a wooden Ayres spatula and an endocervical brush, was classified according to the Bethesda 2001 classification system.[20] Referral for colposcopy was performed for all women at baseline (irrespective of cytology results) and after any abnormal cytology during follow-up. Endocervical samples were collected with sterile swabs or brushes, disposed in Digene HPV Hybrid Capture Universal Collection Medium (UCM1) and immediately frozen until processing. HPV baseline status was determined by Hybrid Capture II (Digene Inc, Gaithersburg, MD, USA). Low-risk HPV (LRHPV) types were: 6, 11, 42, 43 and 44; HRHPV were: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68. CD4+ counts (FACScan; Becton Dickinson and Co, Sparks, MD, USA), viral load measurements, and ART information were systematically obtained from the participant's medical record as per procedures of the INI's HIV cohort.[21]

The study population included adult women (age ≥ 18 at cohort enrollment) enrolled in the cohort from its inception date to December 31 2012. Inclusion criteria for this analysis were: (1) a normal cervical cytology at baseline, and (2) an HRHPV testing result available at baseline. Exclusion criteria were as follows: (1) previous hysterectomy or cervical treatment (such as, cervical cauterization and loop electrosurgical excision procedure), (2) previous HPV vaccination, and (3) having baseline information only. Start of follow-up was defined by cohort entry date and end of follow-up was defined, for those who had an outcome, as the date of the outcome. Participants who underwent hysterectomy/cervical treatment or HPV vaccination were censored at their treatment/vaccination date. Additionally, those who were lost to follow-up (no medical visits and/or new cytology result prior to 2012) and those who died were censored at their last study visit.

Study outcomes and definitions

The outcomes of interest were the occurrence of the first incident abnormal cytology after baseline. Results were reported for: any squamous intraepithelial lesion (referred to as 'any SIL') and any high-grade squamous lesion (referred to as 'HSIL+', which included HSIL, atypical squamous cells, cannot exclude HSIL [ASC-H], and cancer). We calculated incidence rates and risk for both outcomes. Only the first event of each outcome was considered in the analysis. Our main predictor was HRHPV status at baseline. Additional baseline characteristics were as follows: age (continuous variable), self-reported race/color, schooling, age at first sex, number of sexual partners in lifetime and in the last 6 months, smoking status (never, former or current), current hormonal contraception,

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