



Rates and determinants of incidence and clearance of cervical HPV genotypes among HIV-seropositive women in Pune, India

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ABSTRACT

Background: Several studies in recent years have documented the genotype-specific prevalence of HPV infection and wide diversity and multiplicity of HPV genotypes among HIV-seropositive women. Yet, information on changes in HPV genotype-specific incidence and clearance rates over time, and their correlation with clinical or immunologic factors among HIV-seropositive women is scarce.

Objectives: We conducted a prospective study to investigate the incidence and clearance rates of cervical HPV genotypes among HIV-seropositive women in India and expand the evidence base in this area of research.

Study design: Cervical samples were collected from n = 215 HIV-seropositive women in Pune, India who underwent two screening visits separated by a median of 11-months (interquartile range: 8–18 months). HPV genotypes were determined by Roche Linear Array HPV assay. Individual genotype-specific and carcinogenicity-grouping-specific HPV incidence and clearance rates were calculated and the associations between incidence/clearance and age and HIV-related metrics were explored.

Results: Incidence and clearance rates for ‘any HPV’ and ‘carcinogenic HPV’ genotypes were 11.1 and 18.3, and 6.7 and 33.8, per 100 person-years, respectively. Incidence and clearance rates for HPV genotypes of alpha-9 species (HPV16, HPV31, HPV33, HPV35, HPV52 and HPV58) and alpha-7 species (HPV18, HPV39, HPV45, HPV59 and HPV68) were 5.8 and 2.04, and 32.1 and 53.5, per 100 person-years, respectively. Clearance of any HPV type was associated with increasing age of participants (odds ratio: 1.08, 95%CI: 1.004–1.17), although the association marginally lost its statistical significance when adjusted for CD4 counts and antiretroviral therapy status.

Conclusions: Genotype-specific clearance rates of HPV were higher than corresponding incidence rates. The suggestion of a positive associations of increasing age with HPV clearance points to the need for etiologic studies on age-related hormonal changes on clearance of cervical HPV infection.

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1. Background

Persistent infection with carcinogenic genotypes of the human papillomavirus (HPV) is the established etiological factor of cervical cancer. Cervical cancer is the second most common cancer among women in India with approximately 123,000 new cases and

67,000 deaths occurring annually, accounting for almost a fourth of the global burden [1]. In addition to having a high incidence of cervical cancer (~22 cases per 100,000 per year), India also has a high case burden of human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS) (estimated 2.4 million persons, including ~1 million women living with HIV) [1,5]. HIV-infected (‘HIV-seropositive’) women are at an increased risk of cervical HPV infection and HPV-induced cervical precancerous lesions and invasive cervical cancer as compared to HIV-uninfected women [2–4].

Several studies in recent years have documented the type-specific prevalence of HPV infection and wide diversity and

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multiplicity of HPV genotypes among HIV-seropositive women in India [6–10]. Yet, information on changes in HPV genotype-specific incidence and clearance rates over time, and their correlation with clinical or immunologic factors among HIV-seropositive women has not yet been reported in any study. Such information could help uncover unique aspects of HPV natural history in the context of HIV infection, particularly as HIV-seropositive women are now living longer due to increasing access to affordable antiretroviral therapy. Furthermore, such data can be used as inputs for parameters in cost-effectiveness modelling studies and thus aid in the design and evaluation of primary prevention (i.e., vaccination) and secondary prevention (i.e., screening) programs for cervical cancer for this high-risk population.

2. Objectives

We conducted a prospective study to investigate the incidence and clearance of HPV genotypes among HIV-seropositive women in India and expand the evidence base in this area of research.

3. Study design

Study participants were enrolled in an observational study carried out in an outpatient gynecology clinic in a tertiary care hospital in Pune, India as part of the NIH-ICMR funded India-US HIV-Cervical Cancer Prevention Research Consortium. Written, informed consent was obtained from all participants. The description of the study population and the HPV genotyping results at baseline has been published in an earlier report [8]. Participants enrolled in this study were invited to return for clinical follow-up after 12 months of their initial visit. The study period included the follow-up time between the baseline ('start-of-study') and the follow-up ('end-of-study') visits.

During both visits, all women underwent a complete physical, pelvic, and colposcopy examination. Trained nurses collected cervical samples that were used for conventional cytology assessment as well as HPV testing. HPV genotyping was done on cervical specimens using polymerase chain reaction (PCR)-based amplification of target DNA using the Linear Array HPV genotyping test assay (Roche Molecular Systems, Pleasanton, CA, USA). HPV genotypes were classified as 'carcinogenic', 'possibly-carcinogenic', and 'non/unknown-carcinogenic' as per the most recent WHO/IARC classification of HPV carcinogenicity [11].

Incidence and clearance rates of HPV infection were analyzed for all women who attended the follow-up visit, for individual HPV genotypes as well as specific groupings of HPV genotypes. These genotype-groupings included those for 'any HPV', 'carcinogenic HPV', a combined grouping of 'possibly-carcinogenic HPV' and 'non/unknown-carcinogenic HPV', 'single carcinogenic HPV', 'multiple carcinogenic HPV', 'alpha-9 HPV species' (i.e., HPV16 and related types of the alpha-9 species, i.e., HPV31, HPV33, HPV35, HPV52 and HPV58) and 'alpha-7 HPV species' (i.e., HPV18 and related types of the alpha-7 species, i.e., HPV39, HPV45, HPV59 and HPV68), and carcinogenic HPV types covered by the current bivalent/quadrivalent and nonavalent HPV vaccines.

Genotype-specific (and grouping-specific) incidence was defined as detection of a specific individual genotype (and *at least one* of the HPV genotypes in the respective grouping) at the end-of-study visit among women free from infection of that genotype (and *any* genotype in that grouping) at baseline. Genotype-specific (and grouping-specific) clearance was defined as absence of the specific individual HPV genotype (and *all* HPV genotypes in the respective grouping) at the end-of-study visit among women initially infected with that specific genotype (and *at least one* of the genotypes in that grouping) at baseline.

The associations between key factors and the odds of having an outcome of incident or cleared infection at the follow-up visit in the 'any HPV' grouping was evaluated in univariate and multivariable logistic regression models to estimate the crude and adjusted odds ratio (OR) and the corresponding 95% confidence intervals (95%CI).

4. Results

Among 278 HIV-seropositive women who underwent screening at baseline, 215 (77.3%) women attended the follow-up visit; with no significant differences in the characteristics of women who attended and did not attend the follow-up visit. Thus, $n = 215$ represents the study population for this prospective analysis evaluating HPV status differences at the start-of-study visit vs. the end-of-study visit, with variable duration of follow-up time contributed by individual participants. The median age of the participants at baseline was 31 years (inter-quartile range [IQR], 29 to 36 years) and the median time between baseline and follow-up visits was 11 months (IQR: 8–18.3 months). The participants had a median CD4+ cell count of 386/ μL (IQR: 236–554) at baseline, which was significantly lower ($p = 0.001$) for women with HPV (322/ μL) than women without HPV (441/ μL). A total of 58.1% (125/215) participants were on antiretroviral treatment (ART) at baseline, but there was no difference among women with and without HPV ($p = 0.782$).

Table 1 shows the genotype-specific and grouping-specific HPV incidence rates among women who were HPV negative at the start-of-study visit. The overall incidence rate for any HPV genotypes in this cohort was 11.1 per 100 person-years, with 12 women out of the 104 women who were HPV-negative at the start of the study developing new (incident) HPV infections over the 108 person-years of follow-up. There were a total of 16 new HPV types detected in these 12 women.

The incidence rates for the carcinogenic HPV and the possibly/non/unknown carcinogenic HPV genotype-specific groupings were 6.7 and 3.2 per 100 person-years respectively. The genotype-specific incidence rates ranged between 0.47 and 2.75 for carcinogenic genotypes, between 0.45 and 0.93 for possibly-carcinogenic genotypes, and between 0.46 and 1.89 for the non/unknown-carcinogenic HPV genotype groupings. The carcinogenic genotypes HPV58 and HPV16, possibly-carcinogenic genotypes HPV66 and HPV70 and the non-carcinogenic genotypes HPV42 and HPV84 had the highest incidence rates. The incidence rates for alpha-9 and alpha-7 HPV species were 5.8 and 2.04 per 100 person-years respectively.

Table 1 also shows the individual genotype-specific and grouping-specific HPV clearance rates among women who were HPV positive at the start-of-study visit. The overall clearance rate reflecting complete clearance for any HPV infection was 18.3 per 100 person-years, with 21 women out of the 111 women who were HPV-positive at the start of the study clearing HPV infections over the 115 person-years of follow-up. There were a total of 231 any HPV types in these 111 women at the start of study visit of which 51 were cleared at the end of the study visit.

The clearance rates for carcinogenic HPV and possibly/non/unknown-carcinogenic HPV genotype groupings were 33.8 and 51.4 per 100 person-years respectively. The genotype-specific clearance rates per 100 person-years ranged between 28.5 and 100 for carcinogenic HPV, between 33.3 and 100 for possibly-carcinogenic HPV, and between 16.6 and 100 for non/unknown-carcinogenic HPV genotype groupings. The carcinogenic genotype HPV45, possibly-carcinogenic genotypes HPV26, HPV67, HPV73 and HPV82 and the non/unknown-carcinogenic genotypes HPV6, HPV11, HPV40, HPV55, HPV83 and HPV539 had clearance rates of 100%. The clearance rates for genotypes of

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