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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.

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COMPETING INTERESTS

The Authors have no Conflicts of Interests to declare.

ETHICAL APPROVAL

The study protocol was approved by the Ethics Committee of the National AIDS Research Institute, Pune, India. All participants gave written, informed consent.

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.

Keywords

HPV; HIV; genotypes; incidence; clearance; natural history

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 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.

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.

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).

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 to 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 HPVIS39 had clearance rates of 100%. The clearance rates for genotypes of the alpha-9 and alpha-7 HPV species were 32.1 and 53.5 per 100 person-years respectively.

We explored associations between incidence and clearance rates for the 'any HPV genotype' grouping and three key clinical and immunologic factors known to influence the natural history of HPV infection and the clinical course of HPV infection, viz., age, CD4+ cell counts, and ART status. There was a positive association of increasing age (per-year increase) with clearance of HPV (odds ratio 1.08, 95%CI: 1.004–1.17), although this association marginally lost its statistical significance when adjusted for baseline CD4+ cell counts and ART status (adjusted odds ratio: 1.07. 95%CI: 0.99–1.16) (Table 2).

DISCUSSION

To our knowledge, this is the first report on type-specific incidence and clearance rates of HPV infection among HIV-seropositive women from India and one of the very few studies on this topic from a low or middle-income country setting. Very few longitudinal studies on HPV epidemiology have been conducted in similar settings due to logistical and technical difficulties in the execution of cohort studies especially in recruiting and retaining participants, and the costs and complexities of conducting high quality HPV genotyping assays. In this context, this study fills an important research gap and can add to the global literature on this topic for future pooled analyses.

HIV-seropositive women are at an increased risk of acquiring incident HPV infection as compared to their HIV-seronegative counterparts. The proposed reasons for this include higher rates of sexual exposure, increased likelihood of reactivation of latent infections, and increased susceptibility for HPV infection among HIV-seropositive women.[3,12] We observed an overall incidence rate for 'any HPV' infection as 11.1 per 100 person-years, which is higher than that reported in the only Indian study in HIV-seronegative women (5 per 1000 woman-months, equivalent to 6 per 100 person-years) as well as the rates reported (ranging between 3.1 and 9.5 per 100 person-years) in similar studies among HIV-seronegative women elsewhere.[13–16] On the other hand, as compared to estimates reported in HIV-seropositive women globally, the incidence rate for 'any HPV infection' (11.1 per 100 person-years) and 'carcinogenic HPV infection' (6.7 per 100 person-years) were significantly lower than the corresponding rates (ranging between 57.4–68.9 person-years for 'any HPV', and 8.1–38.2 per 100 person-years for 'carcinogenic HPV').[3,4,15,17–19] We noted a higher incidence rates for carcinogenic types than non-carcinogenic types, a finding in accordance with studies among HIV-seronegative women.[14,20,21] Carcinogenic HPV types specifically those belonging to the alpha-9 species had the highest type-specific incidence rates, which is also consistent with that reported in studies among HIV-seropositive women.[6,19,20]

We report an overall clearance rate for any HPV infection as 18.3 per 100 person-years. The clearance rates observed in our study was significantly lower than reported in studies (68.3 to 80.7%) among HIV-seronegative women.[4,22–25] However previous studies amongst HIV-seropositive women have reported HPV clearance rates that are comparable[16], higher[4,8,23,26] and even lower[19] than ours. As reported in earlier studies, we too observed lower clearance rates in women having infection with carcinogenic HPV types especially the alpha-9 species, compared to the clearance rate among carcinogenic HPV types.[4,15,21,27]

Overall, though, the genotype-specific/grouping-specific clearance rates of HPV were higher than corresponding incidence rates over the same follow-up period. The differences in the point estimates of incidence and clearance rates between studies may be caused due to the differences in the demographic characteristics of the cohort, sampling methods, sensitivity of the HPV detection and genotyping assays, or other relatively less-understood aspects of natural history of HPV infection such as variation in host genetics or mucosal immunologic responses modulating HPV co-infection in HIV-seropositive women. It could also be speculated that the lower HPV incidence rates are directly reflective of a modifying factor such as changes in sexual behavior. This is particularly relevant for the majority of HIV+ women in this study who report one lifetime sexual partner who might experience changes in sexual behavior (e.g., increased condom use) as a consequence of them being HIV-infected. It should be noted that the overall grouping-specific rates varied considerably vs. individual type-specific rates for both incident and cleared infections. This was expected since the definition of grouping-specific incidence and clearance rates included consideration of detection of '*at least one*' of the types in the respective grouping (for incidence) and non-detection of '*all* types' in the respective grouping (for clearance).

In the present study, we observed that increasing age was independently associated with increased HPV clearance. There could be several explanations for this finding, including humoral or cellular immune responses that increase with age (presumably correlated with longer time since initial HPV infection), hormonal changes associated with perimenopause/menopause, or the much lesser-studied hormone-immune interactions. This finding needs further exploration in etiologic studies. Evidence of higher HPV clearance in women older than 45 years as compared to those less than 25 years of age is relatively scarce.[12] On the other hand, poorer HPV clearance in women older than 45 years as compared to those less than 20 years of age,[28] decreased HPV clearance with increasing age,[22,29] and even no difference in clearance rates among different age cohorts has been reported previously.[25,30–32] Treatment of HIV infection with antiretroviral therapy at baseline was not statistically significantly associated with increased clearance.. There is limited and conflicting data on the effect of antiretroviral treatment on HPV clearance. Our finding is similar to reports that have shown no protective effect of ART on HPV clearance[33,34] and contrary with studies that show greater HPV clearance with the institution of ART.[35–37]

Our study had some limitations. As is common with HPV natural history studies, our data suffered from left truncation bias, i.e., since our study design was limited to one follow-up visit only, we had to use prevalent cases of HPV infections to assess HPV clearance at the next visit. It would have been preferable to have data from at least three visits, identify incident cases and follow them over time to assess clearance. Also, given the relatively long

time period between the two sampling visits, an interval sampling bias could have been introduced that limited our ability to study the incidence and clearance of HPV DNA genotypes in the interim, particularly in participants who underwent dynamic changes in their immune status due to modifications of antiretroviral therapy medications.

In summary, this study provides the first assessment of the incidence and clearance of type-specific cervical HPV infection among HIV-seropositive women from India. We observed an overall higher genotype-specific clearance rates than the corresponding incidence rates; although we observed a higher incidence and lower clearance for carcinogenic HPV, especially the alpha-9 species, in comparison with possibly/non-carcinogenic genotypes. The evaluation of effectiveness of HPV prevention interventions in resource-constrained countries with high HIV burden is dependent on the knowledge of natural history of HPV in the setting of HIV. The findings from this study will inform design of rational cervical cancer prevention strategies in this population and will contribute to future worldwide pooled analyses on this topic.

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Highlights

- Data on HPV incidence/clearance rates in HIV+ women over median 11-months follow-up
- Genotype-specific HPV clearance rates are higher than corresponding incidence rates
- Marginally significant increase in cervical HPV clearance with increasing age

Table 1

HPV genotype-specific and HPV genotype-grouping-specific incidence and clearance among HIV-seropositive women (n=215) in Pune, India

	Incidence analysis				*Clearance analysis*			
HPV type	**HPV negative at start-of-study visit**	**HPV positive at end-of-study visit ('Incident')**	**Person years**	**Incidence rate (95%CI) per 100 person-years**	**HPV positive at start-of study visit**	**HPV negative at end-of-study visit ('Cleared')**	**Person years**	**Clearance rate (95%CI) per 100 person-years**
HPV genotype groupings								
Any HPV	104	12	108	11.1 (5.7–19.4)	111	21	115	18.3 (11.3–27.9)
Carcinogenic HPV	142	10	149	6.7 (3.2–12.3)	73	25	74	33.8 (21.9–49.9)
Possibly/Non-carcinogenic HPV	183	6	189	3.2 (1.1–6.9)	32	18	35	51.4 (30.4–81.3)
Single carcinogenic HPV	162	9	169	5.3 (2.4–10.1)	53	20	54	37 (22.6–57.2)
Multiple carcinogenic HPV	195	1	203	0.5 (0.01–2.7)	20	5	20	25 (8.1–58.3)
Alpha-9 types (HPV16-related)	163	10	171	5.8 (2.8–10.7)	52	17	53	32.1 (18.7–51.4)
Alpha-7 types (HPV18-related)	188	4	196	2.0 (0.5–5.2)	27	15	28	53.5 (29.9–88.4)
Bivalent/quadrivalent vaccine types (HPV16/18)	183	7	191	3.7 (1.5–7.6)	32	11	32	34.4 (17.1–61.5)
Nonavalent vaccine types (HPV 16/18/31/33/45/52/58)	162	8	169	4.7 (2.0–9.3)	53	16	54	29.6 (16.9–48.1)
Carcinogenic HPV types								
HPV16	190	5	199	2.51 (0.8–5.8)	25	10	24	41.6 (19.9–76.6)
HPV18	206	2	214	0.93 (0.1–3.3)	9	3	10	30 (6.2–87.6)
HPV31	208	0	216	-	7	2	7	28.6 (3.4–103)
HPV33	211	2	219	0.91 (0.1–3.2)	4	2	4	50 (6.1–18)
HPV35	207	2	216	0.93 (0.1–3.3)	8	5	8	62.5 (20.3–146)
HPV39	206	1	214	0.47 (0.01–2.6)	9	7	9	77.8 (31.3–160)
HPV45	212	0	220	-	3	3	3	100 (20.6–292)
HPV51	206	1	214	0.47 (0.01–2.6)	9	6	9	66.7 (24.5–145)
HPV52	203	2	211	0.94 (0.1–3.4)	12	7	13	53.8 (21.6–110)
HPV56	208	3	216	1.39 (0.2–4.0)	7	4	8	50 (13.6–128)
HPV58	210	6	218	2.75 (1.0–5.9)	5	2	5	40 (4.8–144)
HPV59	210	2	219	0.91 (0.1–3.2)	5	2	5	40 (4.8–144)
HPV68	212	0	220	-	3	1	3	33.33 (0.8–185)

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	Incidence analysis				*Clearance analysis*			
HPV type	**HPV negative at start-of-study visit**	**HPV positive at end-of-study visit ('Incident')**	**Person years**	**Incidence rate (95%CI) per 100 person-years**	**HPV positive at start-of study visit**	**HPV negative at end-of-study visit ('Cleared')**	**Person years**	**Clearance rate (95%CI) per 100 person-years**
Possibly-carcinogenic HPV types								
HPV26	215	0	221	-	2	2	2	100 (12–361)
HPV53	203	1	207	0.48 (0.01–2.6)	12	9	17	52.9 (24–100)
HPV66	200	2	215	0.93 (0.1–3.3)	15	3	9	33.3 (6.8–97.4)
HPV67	217	0	222	-	8	1	1	100 (2.5–557)
HPV70	214	2	219	0.91 (0.1–3.2)	1	0	1	-
HPV73	211	0	219	-	4	4	4	100 (27–256)
HPV82	213	1	221	0.45 (0.01–2.5)	2	2	2	100 (12–361)
Non-carcinogenic HPV types								
HPV6	214	0	222	-	1	1	1	100 (2.5–557)
HPV11	214	0	222	-	1	1	1	100 (2.5–557)
HPV40	214	0	223	-	1	1	1	100 (2.5–557)
HPV42	204	4	212	1.89 (0.5–4.8)	11	2	12	16.7 (2–60.2)
HPV54	210	4	218	1.83 (0.5–4.6)	5	3	5	60 (12–175)
HPV55	214	2	222	0.9 (0.1–3.2)	1	1	1	100 (2.5–557)
HPV61	207	3	215	1.4 (0.2–4.0)	8	4	8	50 (13.6–128)
HPV62	197	3	204	1.47 (0.3–4.2)	18	5	19	26.3 (8.5–61.4)
HPV64	213	0	221	-	2	1	2	50 (1.3–278)
HPV71	201	2	209	0.96 (0.1–3.4)	14	4	14	28.6 (7.7–73.2)
HPV72	205	0	214	-	10	4	9	44.4 (12.1–113)
HPV81	210	1	218	0.46 (0.01–2.5)	5	0	5	-
HPV83	214	1	222	0.45 (0.01–2.5)	1	1	1	100 (2.5–557)
HPV84	210	4	218	1.83 (0.5–4.6)	5	3	6	50 (10.3–146)
CP6108	210	1	218	0.46 (0.01–2.5)	5	3	5	60 (12.4–175)
IS39	214	2	222	0.9 (0.1–3.2)	1	1	1	100 (2.5–557)

Table 2

Multivariable models exploring factors associated with incidence and clearance of HPV infection (‘any HPV’ genotype) among HIV-seropositive women (n=215) in Pune, India

	Incidence analysis		Clearance analysis	
Characteristics	***Unadjusted (crude) Odds Ratio (95% CI)***	***Adjusted Odds Ratio (95% CI)***	***Unadjusted (crude) Odds Ratio (95% CI)***	***Adjusted Odds Ratio (95% CI)***
Age (per 1-year increase)	0.94 (0.83–1.07)	0.93 (0.81–1.06)	***1.08 (1.004–1.17)***	1.07 (0.99–1.16)
Currently on ART (vs. not)	3.83 (0.82–17.91)	4.46 (0.92–21.59)	2.49 (0.88–7.08)	2.16 (0.74–6.27)
CD4/μL (per 100-unit increase)	1.27 (0.99–1.63)	1.29 (0.99–1.67)	1.05 (0.85–1.30)	1.05 (0.85–1.31)

Footnote: statistically significant association is bolded and italicized ($p<0.05$). The ‘n’ for age and ART =215 and for CD4+ count=207.