Prevalent and Persistent Oncogenic HPV Types in a Cohort of Women Living with HIV Prior to HPV Vaccination

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Synopsis: Among 252 WLWH in Canada, 17% had persistent infection with non-vaccine oncogenic HPVs. Lower CD4 count predicts persistence.

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Abstract

Objective: To describe prevalent and persistent oncogenic HPV types detected in women living with HIV (WLWH) in Canada, including in women with cervical dyskaryosis, and to determine predictors of type-specific HPV persistence.

Methods: 252 women were eligible for this sub-analysis of a prospective vaccine immunogenicity cohort study (2 HPV DNA results, ≥1 cervical cytology result pre-vaccination). Demographic and clinical data were collected alongside cervical samples for cytology and HPV DNA typing between 2008-2015.

Results: Pre-vaccination, HPV16 and HPV52 were the most prevalent oncogenic HPV types. Forty-five percent of participants were infected with ≥1 oncogenic HPV type and one-third of participants had a persistent oncogenic infection. HPV16, 45, and 52 were the most frequently persistent types. Seventeen percent of women had persistent infections with oncogenic HPV types not within currently available vaccines (HPV35/39/51/56/59/68/82). Lower CD4 count significantly predicted HPV persistence (p=0.024). Cervical cytology was 82.9% normal, 2.4% atypical squamous cells of undetermined significance, 11.5% low-grade squamous intraepithelial lesions, and 2.8% high-grade squamous intraepithelial lesions.

Conclusion: Unvaccinated WLWH were infected with a wide range of oncogenic HPV types. Our findings highlight the importance of optimal HIV treatment and continued cervical cancer screening as key steps towards global elimination of cervical cancer.

Introduction

Cervical cancer remains a leading cause of mortality for women throughout the world due to lack of comprehensive screening and treatment, and limited implementation of vaccine programs globally.[1, 2] Women living with HIV (WLWH) experience approximately double the prevalence of HPV infection compared to their HIV-negative counterparts.[3, 4] In addition, WLWH are more likely to experience infection with less common HPV types, concurrent infections with multiple types, and persistent infection.[5, 6] Collectively, these factors contribute to the higher rates of cervical cancer in WLWH, compared to women without HIV. Data from North America has shown that the incidence rate of cervical cancer among women without HIV is 5 per 100 000 person-years, while in WLWH it is 16 per 100 000 person-years.[7]

Three prophylactic HPV vaccines have been used in vaccination programs over the last decade. The bivalent vaccine (bHPV, Cervarix®, GlaxoSmithKline Inc., Research Triangle Park, NC 27709, USA) provides protection against HPV16/18 and the quadrivalent vaccine (qHPV, GARDASIL™, Merck, Sharp, & Dohme Corp., Whitehouse Station, NJ 08889, USA) protects against HPV6/11/16/18. A nonavalent HPV vaccine (9vHPV, GARDASIL®9, Merck, Sharp, & Dohme Corp., Whitehouse Station, NJ 08889, USA) was more recently licensed and protects against HPV6/11/16/18/31/33/45/52/58. While these vaccines have proven safe and highly efficacious in HIV-negative populations,[8-10] their efficacy in individuals living with HIV is less well established.[11, 12]

When making public health decisions regarding which vaccine is ideal for WLWH and HPV type-based triage in HPV-based cervical screening programs, it is crucial to consider the type-specific HPV prevalence in populations living with HIV. With more comprehensive and successful management of HIV and the introduction of HPV vaccines into routine use, existing data on HPV types in persons living with HIV may be outdated.[3, 13, 14] It is consequently critical to understand the current burden of oncogenic HPV infection in WLWH who are engaged in care and accessing combination antiretroviral therapy. In this analysis, we assessed the prevalence, persistence, and predictors of oncogenic HPV infection prior to vaccination and determined rates of high grade cervical cytology and its relationship to specific HPV types in a cohort of WLWH in Canada.

Materials and Methods

Girls and women living with HIV (WLWH), aged 9 and greater, were recruited into a prospective study of HPV vaccination from 14 sites of HIV care across Canada. All study participants initiated the study with a screening visit and then a baseline visit 3 months later, at the end of which the vaccine series was initiated. They then were offered 3 doses of the quadrivalent HPV vaccine at 0, 2, 6 months followed by visits at 7, 12, 18, and 24 months for the purposes of safety, immunogenicity, and efficacy endpoint assessments. The analysis reflected in this paper is restricted to HPV and cervical cytology data from the 2 pre-vaccine

visits for the purposes of determining the prevalence of HPV infection and cervical cytopathology in this cohort of WLWH in Canada in the era of effective antiretroviral therapy. Therefore, all participants were HPV vaccine-naïve in the study visits included in this analysis. As there was no maximum age for this study, the vaccine was used beyond the age limit of FDA approval. Participants were ineligible if they had received any prior doses of HPV vaccine, had an allergy to vaccine components, were currently enrolled in another study of an investigational drug or vaccine, or if a site investigator deemed their health to be exclusionary. Further details of the study and methods have been previously published.[11, 15] Ethical approval for the coordination of this study was received from the University of British Columbia Clinical Research Ethics Board (H08-00997) and each clinical recruitment site received local ethics approval. All participants provided voluntary written informed consent prior to participation in the study. The study took place between 2008-2015.

For this analysis we utilized two time points, the screening and baseline study visits, planned at three month intervals but with an actual median of four months apart (range: 3-22 months). At both of these study visits, participants underwent a clinical assessment, a pregnancy test, study blood work, cervical cytology, and HPV DNA sampling. Cervical cytology samples utilized liquid-based cytology. These cytology samples were processed by a single reference laboratory at the British Columbia Cancer Agency and were reported using Bethesda criteria. Aliquots of the cytology samples were sent to a single laboratory for HPV DNA

testing using the Linear array assay to provide a positive or negative result for 36 types of HPV as described previously.[16]

The objectives of this analysis were to assess cervical cytology results and their relationship to oncogenic HPV types detected in our cohort prior to vaccination, to determine predictors of type-specific HPV persistence between two visits, and to determine the attributable HPV types in cases of high-grade cervical cytology. 420 participants were enrolled in the study, of which 252 were eligible for this analysis. Participants were eligible if they had two pre-vaccination HPV DNA results that were at least 3 months apart and at least one pre-vaccination cervical cytology result. All statistical analyses were performed in R (version 3.2.2). Oncogenic HPVs were divided into categories based on their presence in currently available HPV vaccines. Logistic regression was utilized for both univariate and multivariate analysis. All variables that were significant upon univariate analysis were included in the multivariate model. P-values below 0.05 were considered statistically significant.

Results

The median age was 39 years (IQR: 33-45, range: 16-65) with mixed ethnicity: predominantly Black (111 [44.0%]) and White (91 [36.1%]) ethnicities, 32 (12.7%) Indigenous, and 18 (7.1%) other. The median number of lifetime sexual partners was 6 (IQR: 3-12). The most frequently self-reported mode of HIV acquisition was sexual contact (187 [74.2%]). In terms of antiretroviral use, 217 (86.1%) of

participants were on a regimen, 19 (7.5%) were not on therapy, and 16 (6.3%) had unknown antiretroviral use status. Of those on antiretrovirals, 123 (56.7%) were on protease inhibitor (PI)-based regimens and 66 (30.4%) on non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens. The median CD4 count at baseline was 510 cells/mm^3 (IQR: 388-698, range: 11-1610) and the median CD4 nadir was 240 cells/mm^3 (IQR: 111-340, range: 0-1078). One hundred and eighty (72.9%) of 247 participants with HIV viral loads available were HIV virologically suppressed (<50 copies/mL) at baseline. Thirty-eight (16.1%) of 236 participants with hepatitis C results available were co-infected with hepatitis C virus.

At the baseline visit, HPV16 and HPV52 were the most prevalent oncogenic HPV types (26 [10.3%] and 23 [9.1%], respectively). The next most prevalent types, in order of most to least prevalent, were HPV45, 51, 56, 58, 59, and 18. HPV16, 52, and 45 were also the most frequent types associated with persistent infection between the screening and baseline visits (19 [7.5%], 16 [6.3%], and 16 [6.3%], respectively). The additional HPV types contributing to persistent infection, in order of most to least frequent, were HPV56, 58, 35, 39, 18, 51, and 59. Overall, almost half of the population (114 women [45.2%]) was infected with at least one oncogenic HPV type at baseline and 84 (33.3%) participants had a persistent oncogenic infection between the two study visits.

Oncogenic HPV types were also divided into categories based on their presence in available vaccines. These categories were: HPV16, HPV18, additional nonavalent types (HPV31/33/45/52/58), and other high-risk types (HPV35/39/51/56/59/68/82) which are not protected against by any vaccine. 19 (7.5%) participants had a persistent HPV16 infection, 8 (3.2%) had a persistent HPV18 infection, 45 (17.9%) had a persistent infection with at least one of the additional nonavalent HPV types (HPV31/33/45/52/58), and 43 (17.1%) had persistent infections with at least one oncogenic HPV type not contained in any currently available vaccine (HPV35/39/51/56/59/68/82).

Hypothesis testing was not performed for HPV18 due to the low number of cases. Univariate analyses of potential predictors of HPV persistence demonstrated no significant difference between women with and without persistent oncogenic HPV infection in demographic variables (including age, ethnicity, lifetime sexual partners, and region of origin) or hepatitis C status, aside from lower age being associated with HPV16 persistence (p=0.037, OR=0.95 [95% CI: 0.89-0.99]). Women with persistent HPV16 and persistent other high-risk HPV were more likely to have an unsuppressed HIV viral load of >50 copies/mL (p=0.016, OR=3.24 [95% CI: 1.25-8.53] and p=0.026, OR=2.20 [95% CI: 1.10-4.35], respectively). Relatedly, women with persistent other high-risk HPV types were more likely to have a lower CD4 count (p=0.012, OR=1.00 [95% CI: 1.00-1.00]).

Multivariate analysis was not performed for HPV16 persistence due to the low number of cases. In multivariate logistic regression for other high-risk type persistence, only CD4 count remained a significant predictor of persistence (p=0.024). The odds of other high-risk HPV persistence are 16% lower for every 100 unit increase in CD4 count, after adjustment for viral load suppression.

The baseline cervical cytology within our cohort was 82.9% (n=209) normal, 2.4% (n=6) atypical squamous cells of undetermined significance (ASCUS), 11.5% (n=29) low-grade squamous intraepithelial lesions (LSIL), 0.4% (n=1) atypical squamous cells – cannot exclude HSIL (ASC-H) and 2.8% (n=7) high-grade squamous intraepithelial lesions (HSIL). Of the seven HSIL cases observed, there were two in which only HPV35 was detected, one in which only HPV52 was detected, and one in which only HPV33 was detected. In three of the cases, multiple HPV infections were detected with the types listed in Table 4.

Discussion

In this cohort of 252 WLWH, the oncogenic HPV types responsible for the highest frequencies of persistent infections were HPV16, 45, and 52, which are all contained in the nonavalent vaccine. However, we observed persistent infection with oncogenic HPV types not contained within any currently available vaccine. These types included HPV56, 35, 39, 51, and 59 which were persistent in 12 (4.8%), 9 (3.6%), 9 (3.6%), 8 (3.2%), and 8 (3.2%) of women in the study, respectively. While these HPV types contribute less to cervical cancer than the

types contained within available vaccines, HIV infection may increase the pathogenicity of these less common types in WLWH due to known interactions between HPV and HIV at the cervix.[17, 18]

The rates of cytological outcomes seen in this population are similar to those seen in other engaged, North American populations of WLWH around the time of combination antiretroviral therapy (cART) implementation.[3] As the cases of HSIL cytology are the closest surrogate for cervical pre-cancer/cancer outcomes, the HPV types present in these cases were of particular interest.

Although based on a small number of HSIL cytology cases, in our cross-sectional cytology analysis, only a maximum of two out of seven (28.6%) of our HSIL cases were associated with highly oncogenic HPV16. We found that the other high-risk types were the cause of at least two out of seven (28.6%) of HSIL in our WLWH. Due to their presence in multiple-type infections, other high-risk types may have been responsible for up to four out of seven (57.1%) of the HSIL cytology cases. The relatively high rates of other high-risk types associated with HSIL cytology in this cohort, combined with relatively low rates of HPV16, are in accordance with literature that has found higher rates of less common oncogenic HPV types in WLWH compared to their HIV-negative counterparts.[14, 19] This also supports the hypothesis that HPV16 has a reduced competitive advantage in the context of HIV infection and associated immune suppression.[14]

The association of persistent other high-risk HPV infection with lower CD4 counts, a measure of immune function, reflects the importance of the immune system in clearing HPV infections rapidly prior to the establishment of persistence. CD4 count and HIV viral load are intrinsically related, which explains the association to HIV viral load suppression seen in the univariate analyses for both HPV16 and other high-risk HPV persistence. Beyond the surrogacy of these measures for immune function, there may be an important role of virus-virus interactions in persistent infection. This may be related to the ability of HIV to disrupt the epithelial tight junctions, improving the ability of HPV to infect the basal epithelial cells.[20] Additionally, it has been shown that HIV tat protein enhances HPV transcription and the expression of HPV oncogenes.[17] Findings from our study also previously demonstrated that immunogenicity to the quadrivalent HPV vaccine was higher in the context of HIV viral load suppression.[15]

The high rate of persistent infection with HPV31/33/45/52/58 (types contained within the nonavalent vaccine but not within the quadrivalent or bivalent formulations; 17.9%) supports the added value of the nonavalent vaccine for WLWH. Importantly, there was a similar percentage of persistent infections caused by high-risk oncogenic HPVs not contained within any vaccine (17.1%). Thus, regardless of HPV vaccination history, it is critically important for clinicians to continue to offer cervical cancer screening to patients living with HIV.

283 This study provides a national perspective of HPV in WLWH in Canada through
284 its multi-site recruitment. As recruitment for this study occurred in HIV care
285 clinics, the study population was generally well engaged in care and may not be
286 generalizable to a less engaged population. While a strength of this analysis is
287 the longitudinal design, which allowed us to determine persistent infections that
288 are of higher clinical relevance than prevalent infections, this analysis was also
289 limited by the fact that it only assessed two time points for HPV infection and was
290 cross-sectional in its ascertainment of risk of cervical dysplasia by cytological
291 testing. Additionally, the number of cytological HSIL cases was low which
292 prevented us from determining attributable risk for each HPV type.
293
294 Higher CD4 count was associated with lower rates of HPV persistence and
295 presumably lower risk of dysplasia.[21] WLWH who had not yet received HPV
296 vaccine in our study showed a wide range of oncogenic HPV infection,
297 demonstrating the need to continue cervical cancer screening in WLWH
298 regardless of vaccine history. Cervical screening programs utilizing HPV testing
299 should consider all oncogenic HPV types in populations of WLWH and
300 vaccination programs should aim to provide the highest valency vaccines to
301 WLWH. This study informs the path towards global elimination of cervical cancer.
302

303 **Author Contributions**

304 DM conceived and initiated the study and was Principal Investigator. DM, JR, and
305 SW contributed to study design. JR managed the database. FC performed HPV

DNA genotyping. SW, MLoutfy, ST, FS, MK, MH, JC, MY, WW, and DM were lead investigators at the study sites. NL managed the study from the coordinating centre. EM conducted the analyses and wrote the first draft of the manuscript. EM, MLee, and DM interpreted the results. All authors contributed to manuscript editing and approved the final manuscript.

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Conflicts of Interests

Dr. Coutlée has received grants for research projects from Roche Diagnostics, Becton Dickenson, and Merck, Sharp, and Dohme, honoraria for presentations from Merck, Sharp, and Dohme and Roche Diagnostics, and has participated in an expert group by Merck, Sharp, and Dohme, outside the submitted work. Dr. Lee has received honoraria from Merck Canada Inc. Dr. Raboud is a co-

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personal fees for symposium participation from Merck Canada Inc., outside the submitted work. The remaining authors have no conflicts to declare.

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Tables

Table 1: Study Population Characteristics

Characteristic	N (%) or median (IQR)
Age	39 (33-45)
Ethnicity	
Black	111 (44.0%)
Indigenous	32 (12.7%)
White	91 (36.1%)
Other	18 (7.1%)
Region of origin	
Africa	85 (33.7%)
Canada	123 (48.8%)
Other	44 (17.5%)
Probable mode of HIV acquisition	
Blood products	14 (5.6%)
Sexual contact	187 (74.2%)
IDU	40 (15.9%)
MTCT	7 (2.8%)
Other	25 (9.9%)
Women with suppressed HIV viral load at baseline	180 (72.9%)
CD4 count at baseline (/mm^3)	510 (388-698)
CD4 nadir (/mm^3)	240 (111-340)

Table 2: Prevalent and Persistent Infection

Oncogenic HPV Genotype	Prevalent Infection	Persistent Infection
HPV 16	26 (10.3%)	19 (7.5%)
HPV 45	18 (7.1%)	16 (6.3%)
HPV 52	23 (9.1%)	16 (6.3%)
HPV 56	16 (6.3%)	12 (4.8%)
HPV 58	16 (6.3%)	10 (4.0%)
HPV 35	12 (4.8%)	9 (3.6%)
HPV 39	12 (4.8%)	9 (3.6%)
HPV 18	14 (5.6%)	8 (3.2%)
HPV 51	17 (6.7%)	8 (3.2%)
HPV 59	15 (6.0%)	8 (3.2%)
HPV 31	9 (3.6%)	7 (2.8%)
HPV 68	13 (5.2%)	6 (2.4%)
HPV 33	7 (2.8%)	4 (1.6%)
HPV 82	5 (2.0%)	3 (1.2%)
Any oncogenic HPV	114 (45.2%)	84 (33.3%)

Table 3: Analysis of Factors Relating to HPV Persistence

	Persistent Median (IQR) or n (%)	**Non-Persistent** Median (IQR) or n (%)	**Univariate analysis** p-value OR (95% CI)	**Multivariate analysis** p-value OR (95% CI)
HPV16	**N = 19**	**N = 233**		
CD4 count	403 (253-620)	520 (450-620)	p=0.059 1.00 (1.00-1.00)	
CD4 nadir	133 (88-251)	240 (116-342)	p=0.179 1.00 (0.99-1.00)	
HIV viral load suppression			**p=0.016**	
Yes	9 (47%)	172 (74%)	1.00	
No	10 (53%)	59 (25%)	3.24 (1.25-8.53)	
Unknown	0	2 (1%)	n/a	
Age	37 (29-42)	39 (33-46)	**p=0.037** 0.95 (0.89-0.99)	
Ethnicity			p=0.207	
Black	6 (32%)	105 (45%)	0.31 (0.09-1.14)	
Indigenous	5 (26%)	27 (12%)	1.00	
Other	8 (42%)	101 (43%)	0.43 (0.13-1.51)	
Region of origin			p=0.377	
Africa	4 (21%)	81 (35%)	1.00	
Canada	12 (63%)	111 (48%)	2.19 (0.73-8.05)	
Other	3 (16%)	41 (18%)	1.48 (0.28-7.03)	
Total lifetime sexual partners			p=0.737	
<5	6 (32%)	75 (32%)	1.00	
5-25	9 (47%)	92 (39%)	1.22 (0.42-3.79)	
26-99	1 (5%)	18 (8%)	0.69 (0.04-4.43)	
>99	2 (11%)	10 (4%)	2.50 (0.34-12.71)	
Hepatitis C co-infection			p=0.469	
Yes	2 (11%)	36 (15%)	1.00	
No	17 (89%)	181 (78%)	1.69 (0.46-10.96)	
Unknown	0	16 (7%)	n/a	
Additional Nonavalent HPV	**N=45**	**N=207**		
CD4 count	521 (371-674)	513 (380-673)	p=0.677 1.00 (1.00-1.00)	
CD4 nadir	220 (110-328)	240 (116-342)	p=0.900 1.00 (1.00-1.00)	
HIV viral load suppression			p=0.349	
Yes	30 (67%)	151 (73%)	1.00	
No	15 (33%)	54 (26%)	1.40 (0.69-2.76)	
Unknown	0	2 (1%)	n/a	
Age	39 (32-46)	39 (34-45)	p=0.371 0.98 (0.95-1.02)	
Ethnicity			p=0.306	
Black	24 (53%)	87 (42%)	1.20 (0.46-3.50)	
Indigenous	6 (13%)	26 (13%)	1.00	
Other	15 (33%)	94 (45%)	0.69 (0.25-2.10)	

Region of origin Africa Canada Other	 19 (42%) 17 (38%) 9 (20%)	 66 (32%) 106 (51%) 35 (17%)	p=0.252 1.00 0.56 (0.27-1.15) 0.89 (0.35-2.14)	
Total lifetime sexual partners <5 5-25 26-99 >99	 18 (40%) 16 (36%) 3 (7%) 2 (4%)	 63 (30%) 85 (41%) 16 (8%) 10 (5%)	p=0.724 1.00 0.66 (0.31-1.39) 0.66 (0.14-2.25) 0.70 (0.10-2.97)	
Hepatitis C co-infection Yes No Unknown	 7 (16%) 37 (82%) 1 (2%)	 31 (15%) 161 (78%) 15 (7%)	p=0.969 1.00 1.02 (0.44-2.67) n/a	
Other High-Risk HPV	**N=43**	**N=209**		
CD4 count	440 (320-600)	530 (392-696)	**p=0.012** 1.00 (1.00-1.00)	**p=0.024** 1.00 (1.00-1.00)
CD4 nadir	185 (90-294)	249 (120-350)	p=0.178 1.00 (1.00-1.00)	
HIV viral load suppression Yes No Unknown	 25 (58%) 18 (42%) 0	 156 (75%) 51 (24%) 2 (1%)	**p=0.026** 1.00 2.20 (1.10-4.35) n/a	p=0.089 1.00 1.86 (0.91-3.75) n/a
Age	38 (30-46)	39 (34-45)	p=0.437 0.99 (0.95-1.02)	
Ethnicity Black Indigenous Other	 15 (35%) 6 (14%) 22 (51%)	 96 (46%) 26 (12%) 87 (42%)	p=0.401 0.68 (0.25-2.05) 1.00 1.10 (0.42-3.23)	
Region of origin Africa Canada Other	 12 (28%) 24 (56%) 7 (16%)	 73 (35%) 99 (47%) 37 (18%)	p=0.579 1.00 1.47 (0.70-3.23) 1.15 (0.40-3.11)	
Total lifetime sexual partners <5 5-25 26-99 >99	 15 (35%) 15 (35%) 2 (5%) 3 (7%)	 66 (32%) 86 (41%) 17 (8%) 9 (4%)	p=0.671 1.00 0.77 (0.35-1.69) 0.52 (0.08-2.08) 1.47 (0.30-5.63)	
Hepatitis C co-infection Yes No Unknown	 4 (9%) 36 (84%) 3 (7%)	 34 (16%) 162 (78%) 13 (6%)	p=0.226 1.00 1.89 (0.70-6.62) n/a	

Table 4: Attributable HPV in Baseline HSILs

Oncogenic HPV Present	# HSIL Cases
35	2
33	1
52	1
Multiple infection Case 1=16, 35, 56 Case 2=16, 58 Case 3=52, 56	3