Persistence of Non-Vaccine Oncogenic HPV Serotypes in Quadrivalent HPV-Vaccinated Women Living with HIV

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Abstract

Background: HPV vaccines have promising safety and immunogenicity data in women living with HIV (WLWH). However, it is critical to understand the residual burden of oncogenic HPV within WLWH in order to inform post-vaccination cervical screening needs. We assessed rates of persistent infection with non-quadrivalent HPV (qHPV) oncogenic types in a cohort of qHPV-vaccinated WLWH.

Setting: Multi-centre, longitudinal cohort across Canada.

Methods: WLWH were scheduled to receive three doses of qHPV vaccine. Participants provided health data and HPV DNA samples. Persistent cases of HPV were defined as new HPV in samples from ≥2 consecutive visits or as HPV present in the last sample. HPV31/33/35/39/45/51/52/56/58/59/68/82 were considered to have oncogenic potential. Median follow-up time was 4 years post initial vaccine dose.

Results: 284 participants were eligible for this analysis with 1205 person-years (PY) of follow-up (≥1 dose of vaccine, ≥1 HPV DNA result post-vaccination). The highest incidence of persistent infection was with HPV51 (1.38/100PY), followed by HPV52 (1.18/100PY), and HPV39 (1.06/100PY). The incidence of persistent infection with pooled HPV types added in the nonavalent vaccine (HPV31/33/45/52/58) was lower than the incidence of persistent oncogenic HPV types not contained within available vaccines (HPV35/39/51/56/59/68) (2.4/100PY versus 3.6/100PY, respectively).

Conclusions: qHPV-vaccinated WLWH continue to face a burden of persistent oncogenic HPV infection. While the nonavalent vaccine could alleviate some of this burden, two of the top three persistent oncogenic HPVs in this cohort are not contained

within any available vaccine. This highlights the need for ongoing cervical screening in HPV-vaccinated WLWH.

Keywords: HPV vaccine, HIV, HPV, cervical cancer, women

Background

Human papillomavirus (HPV) disproportionately affects women living with HIV (WLWH) resulting in a much larger burden of HPV-associated disease, such as cervical cancer, than that seen in the general population. The prevalence of HPV infection among WLWH is approximately 50%, which is twice the prevalence in women without HIV.[1] The rate of persistent HPV infection among WLWH is approximately 20-24%, making WLWH 3-6 fold more likely to have a persistent HPV infection than women without HIV.[2,3] The disparity between rates of cervical cancer is equally wide; within a North American population of WLWH, the incidence rate of invasive cervical cancer (i.e. cervical cancer that has invaded into deeper layers of the cervix beyond the surface) was 16 per 100 000 person-years, compared to only 5 per 100 000 person-years in women without HIV.[4]

In addition to higher rates of HPV-related infection and disease, WLWH also experience infection with a wider range of HPV types,[5] which has important implications for vaccine and cervical screening programming. HPV16 is well known to be the most carcinogenic of HPV types. However, it is less affected by increased immunodeficiency than other oncogenic HPVs and is also seen in a reduced proportion among WLWH.[6]

Although HPV vaccines are now available and have promising safety and immunogenicity findings in WLWH to date,[7-10] it is critical to identify the residual burden of oncogenic HPV within WLWH in order to inform post-vaccination cervical screening needs for this population. In this study, we assessed rates of new persistent

infection with oncogenic HPV types not contained in the quadrivalent HPV (qHPV) vaccine in our cohort of qHPV-vaccinated WLWH.

Methods

As part of a longitudinal study of HPV vaccine immunogenicity and efficacy, girls and WLWH aged nine and greater were recruited from 14 clinics serving WLWH across Canada between 2008-2012, with long term follow-up to six years. All participants or guardians, as appropriate, provided informed consent to enroll in the study. The study population and methods of enrolment have previously been described.[7] Participants were scheduled to receive three doses of qHPV vaccine intramuscularly at month 0/2/6. Serology for anti-qHPV antibodies was performed by competitive Luminex immunoassay (cLIA) at Merck Research Laboratories. Pelvic examination was performed on participants who were post-menarchal and sexually active at the discretion of the care provider and in accordance with time- and geographic-specific clinical recommendations. For participants undergoing pelvic examination, cervical cytology and cervico-vaginal HPV DNA samples were collected by a health care provider at the screening visit and at months 0/6/12/18/24/36/48/60/72/84/96. The ThinPrep® Pap Test was utilized for collection of cervical cytology samples using a cytobrush and results were classified by Bethesda Criteria centrally at the British Columbia Cancer Agency Cervical Cancer Screening Laboratory. Aliquots of the PreservCyt® from Pap tests were processed and typed for 36 HPV genotypes by Linear array assay (Roche Molecular Systems).[11]

For this analysis, the primary outcome was rate of persistent HPV infection with oncogenic, non-quadrivalent vaccine HPV types (i.e., oncogenic types not including HPV16/18) within our cohort of qHPV-vaccinated WLWH. Persistent HPV infection was defined as the detection of the same incident HPV type in samples collected at two or more consecutive study visits (>6 months apart) or detection of an HPV type at the last available visit. Although this definition of persistent infection is an accepted definition utilized within the HPV vaccine literature,[12,13] it is known to overestimate the true number of persistent infections by including cases where HPV is present only in the last sample; however, it is accepted as it errs on the side of caution since some of these infections will persist. Due to this, a sensitivity analysis was also conducted where only the confirmed persistent cases (i.e., detection of the same HPV type at two or more consecutive study visits) were considered. The final sub-analysis presented herein determines the incidence of persistent infection with HPV types contained only in the nonavalent vaccine (HPV31/33/45/52/58) as compared to the incidence of persistent infection with oncogenic HPV types not contained within available vaccines (HPV35/39/51/56/59/68). To be eligible for this analysis, participants had to have received at least one dose of vaccine and had to have at least one HPV DNA result post-vaccination. For ascertainment of HPV cases, participants were required to be DNA negative to the relevant HPV type at the screening and baseline visits. The HPV types considered in this analysis were HPV31/33/35/39/45/51/52/56/58/59/68; these HPV types were selected for consideration due to their oncogenic potential.[14]

Results

284 participants were eligible for analysis with 1205 person-years of follow-up and a median follow-up time of four years per person. Eligible population characteristics at baseline are described in Table 1. The median age was 38 years (IQR: 32-44). Participants were predominantly of Black (41%) and White (36%) ethnicity. The median CD4 count at first vaccination was 499 cells/mm^3 (IQR: 375-680) and 71% of participants had HIV plasma viral loads <50 copies/ml. 267 participants (94%) received all three doses of vaccine. The vaccine was safe and highly immunogenic within this population, as previously described.[7]

The incidence rates of persistent HPV types are shown in Figure 1. The most frequently documented persistent infections were infections with HPV51 (incidence rate [IR]: 1.4 per 100 person-years [/100PY], 95% confidence interval [CI]: 0.8-2.3). The second and third most common types contributing to persistent infection were HPV52 (IR: 1.2 /100PY, 95% CI: 0.6-2.1) and HPV39 (IR: 1.1 /100PY, 95% CI: 0.6-1.9), respectively. These types were followed by HPV45 (IR: 0.9 /100PY, 95% CI: 0.4-1.7) and HPV35 (IR: 0.7 /100PY, 95% CI: 0.3-1.4) being fourth and fifth most common, respectively. Overall, 40% of persistent infections were cases in which the HPV type was detected in at least two consecutive samples while HPV was detected in the last sample in 60% of cases. This 40%/60% split between confirmed persistent and last sample cases was also consistent within HPV types.

In a sensitivity analysis that limited to only the confirmed persistent cases (not including cases of HPV detection in the last sample), the most frequently documented HPV type

remained as HPV51 (IR: 0.6 /100PY, 95% CI: 0.2-1.2), followed by HPV52 (IR: 0.5 /100PY, 95% CI: 0.2-1.1) and HPV39 (IR: 0.4 /100PY, 95% CI: 0.1-1.0), respectively. In a sub-analysis pooling HPV types into categories of nonavalent (HPV31/33/45/52/58) or oncogenic HPV types not contained within available vaccines (HPV35/39/51/56/59/68), the composite endpoints yielded an incidence rate of 2.4 /100PY (95% CI: 1.6-3.5) for persistent infection with nonavalent HPV types and an incidence rate of 3.6 /100PY (95% CI: 2.6-4.9) for persistent infection with HPV types not contained within vaccines.

Discussion

Of the top five persistent HPV types observed in this cohort, only HPV52 and 45 are contained within the nonavalent vaccine. Additionally, the persistent infection with the HPV types added in the nonavalent vaccine that are not present in the quadrivalent vaccine had an incidence rate of 2.4 /100PY while persistent infection with HPV types not contained within any available vaccine resulted in a higher incidence rate of 3.6 /100PY. This implies that the nonavalent vaccine could further assist in the protection of WLWH, but gaps in protection for this population would remain. Although the HPV types that are not contained within any currently available vaccine contribute less to disease in the general population, they are carcinogenic and the effect of HIV infection on the pathogenicity of these specific HPV types has not been completely elucidated. Description of HPV types associated with CIN3+ in women without HIV and WLWH has shown that the contribution of HPV51 and 39 towards dysplasia in WLWH is greater

194 than in women without HIV.[15] Meta analysis has also shown that WLWH who have
195 HSIL are less likely to be infected with HPV16 than the general population and more
196 likely to be infected with HPV51, among other types, or to have multiple HPV type
197 infection.[6] HIV is known to disrupt epithelial tight junctions, which may facilitate HPV
198 entry to the basal epithelial layer.[16] It is also known that the HIV tat protein enhances
199 HPV transcription.[17] This could be a mechanism explaining the potential oncogenic
200 effects of HPV serotypes that could differentially affect WLWH. As the HPV types not
201 contained within available vaccines may cause disease in this way, it is important to note
202 that the infectivity and carcinogenic potential of these HPV types is enhanced in WLWH.
203 Further study is needed to more clearly describe the contribution of these HPV types to
204 cervical dysplasia among WLWH.
205 The high rate of persistent infection with HPV51 validates previous data indicating that
206 there is a high burden of HPV51 in WLWH and that this type would be very important in
207 WLWH post-vaccination.[18] We observed less persistent HPV31 and HPV33 than
208 reported in some previous studies of North American WLWH.[6,19] However, we did see
209 relatively high rates of persistent HPV52 and HPV58, which is consistent with prior
210 literature in WLWH.[6] We might hypothesize the differences could be a result of some
211 cross-protection against HPV31, which is closely related to HPV16 within the alpha-9
212 phylogenetic group, and HPV33, which is also an alpha-9 HPV type. Evidence of cross-
213 protection against HPV31 and HPV33 by the quadrivalent HPV vaccine has previously
214 been documented.[20]
215 The main analysis was conservative in nature and provides an overestimate of the
216 incidence of persistent infection as not all cases of HPV detected at the last visit will go

on to truly persist. The sensitivity analysis provided the opposite scenario of an underestimate of incidence of persistent infection as it only included cases where the HPV type was documented at two consecutive visits. Taken together, these analyses were consistent in demonstrating that HPV51, 52, and 39 contribute the largest burden of persistent infection among this vaccinated population, and they demonstrate the upper and lower limits within which the true value of incident persistent infections lies. Limitations to this analysis include the fact that our findings may not be generalizable to other global settings due to multiple factors including availability and engagement in HPV vaccination programs, cervical screening programs, and HIV care including antiretroviral use, as well as the geographic distribution of different HPV types. Additionally, these findings pertain to women vaccinated with the quadrivalent HPV vaccine, which is now largely replaced by the more recently available nonavalent vaccine. However, our findings do break down the persistent HPV types based on availability in current vaccines, including the nonavalent vaccine, which addresses this shift in vaccine valency. Nonetheless, findings of the residual burden of oncogenic HPV types 35/39/51/56/59/68 in WLWH vaccinated with the nonavalent vaccine may differ. To our knowledge, only one other paper has described HPV infection with non-vaccine HPV types post-vaccination within a population of WLWH, but women were only followed for one year post-vaccination.[21] Similar to our findings, they reported a higher frequency of the non-vaccine HPV types 51 and 52 detected at 28 and 52 weeks. In contrast to our findings, they detected a relatively high frequency of HPV31 at the 52-week time point and HPV68 at both time points, but not a higher frequency of HPV39.[21] Given the broad range of oncogenic HPV types seen in vaccinated WLWH, cervical

screening will remain important in this population. Additional data is needed to inform programs using HPV DNA testing as a screening modality for WLWH due to the likely altered carcinogenicity of certain HPV types in WLWH.

Conclusions

Our findings add critical data to the literature regarding persistent HPV infection with extended follow up post-vaccination in WLWH. WLWH who have been vaccinated with the quadrivalent HPV vaccine remain vulnerable to a clinically significant burden of persistent HPV infections. The frequency with which these strains lead to cervical dysplasia and cancer requires ongoing study. Although the nonavalent vaccine has the potential to eliminate a portion of that burden, many of the persistent HPV infections that WLWH face are due to HPV types not contained within any currently available vaccine. Our findings support the continued regular cervical screening of WLWH regardless of their HPV vaccine history and validate the need for a multipronged approach to elimination of cervical cancer.

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Details of Ethics Approval

Ethical approval for central study coordination was obtained from the University of British Columbia Clinical Research Ethics Board (approval H08-00997) and all recruiting clinical sites received research ethics approval locally.

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Figure Legends

Figure 1: Non-Vaccine Oncogenic HPV Persistence

Light grey: additional HPV types in the nonavalent vaccine; dark grey: oncogenic HPV types not contained within available vaccines