The Efficacy of the Quadrivalent Human Papillomavirus Vaccine in Girls and Women Living with HIV

Authors: Elisabeth McClymont [a], Marette Lee [a], Janet Raboud [b,c], François Coutlée [d], Sharon Walmsley [b,e], Nancy Lipsky [f], Mona Loutfy [g], Sylvie Trottier [h], Fiona Smaill [i], Marina B. Klein [j], Marianne Harris [k], Jeffrey Cohen [l], Mark H. Yudin [g,m], Wendy Wobeser [n], and Deborah Money [a] for the CTN 236 HPV in HIV Study Team.

[a] Department of Obstetrics and Gynecology, University of British Columbia, Vancouver, BC, Canada [b] Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada [c] Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada [d] Département de Microbiologie Médicale et Infectiologie, l'Université de Montréal, Montréal, QC, Canada [e] Department of Medicine, University of Toronto, Toronto, ON, Canada [f] Women's Health Research Institute, Vancouver, BC, Canada [g] Women's College Research Institute, University of Toronto, Toronto, ON, Canada [h] Infectious Diseases Research Centre – Université Laval, Québec City, QC, Canada [i] Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada [j] McGill University Health Centre, Montreal, QC, Canada [k] British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada [l] Windsor Regional Hospital HIV Care Program, Windsor, ON, Canada [m] Department of Obstetrics and Gynecology, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada [n] Department of Medicine, Queen's University, Kingston, ON, Canada

Corresponding author: D Money, 317 – 2194 Health Sciences Mall, University of British Columbia, Vancouver, BC, Canada, V6T 1Z3. Email: deborah.money@ubc.ca Telephone: 1-604-827-0327.

Alternate corresponding author: E McClymont, B327 – 4500 Oak Street, BC Women, Vancouver, BC, Canada, V6H 3N1. Email: elisabeth.mcclymont@cw.bc.ca Telephone: 1-604-833-1838.

Running title: qHPV Vaccine Efficacy in Women with HIV

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

Abstract

Background: Human papillomavirus (HPV) vaccination is safe and efficacious in women without HIV. While good immunogenicity has been observed in women living with HIV (WLWH), efficacy data in this population are needed.

Methods: We enrolled 420 females aged ≥9 years (range: 9-65) living with HIV. Participants were to receive 3 doses of qHPV vaccine (0/2/6 months). The main endpoint was vaccine failure (i.e., incident persistent qHPV infection, cervical intraepithelial neoplasia of grade 2 or higher (CIN2+), or genital warts). We compared these rates to published rates in vaccinated and unvaccinated women without HIV as well as unvaccinated WLWH.

Results: Among 279 eligible women, median follow-up was 2 years. In the intention-to-treat population, the incidence rate (IR) of persistent qHPV (HPV6/11/16/18) was 2.3 per 100 person-years (/100PY) (95% confidence interval [CI]=1.1-4.1) and IR of genital warts was 2.3/100PY (95% CI=1.2-4.1). In the per-protocol efficacy population, IR of persistent qHPV was 1.0/100PY (95% CI=0.3-2.6) and of genital warts was 1.0/100PY (95% CI=0.3-2.5). No cases of CIN2+ occurred. Reported rates of qHPV-related infection and disease within the vaccinated women without HIV, unvaccinated women without HIV, and the vaccinated WLWH: 0.1 (95% CI=0.02-0.03), 1.5 (95% CI=1.1-2.0), and 1.2 (95% CI=0.2-3.4) /100PY, respectively. The rate of persistent qHPV among vaccinated WLWH was lower than among unvaccinated WLWH (2.3 vs. 6.0/100PY).

Conclusions: Vaccinated WLWH may be at higher risk for vaccine failure than vaccinated women without HIV. However, overall rates of vaccine failure were low and rates of persistent qHPV were lower than in unvaccinated WLWH.

Background

Cervical cancer is a major health burden for women, resulting in over 250 000 deaths globally each year [1]. While low- and middle-income countries bear the greatest burden of disease, with an age-standardized cervical cancer mortality rate of 8.3 per 100 000 population, many women in high-income countries (HIC) also continue to be affected, with a mortality rate of 3.3 per 100 000 [2]. Human papillomavirus (HPV) has been well established as the primary causal agent of cervical cancer, making this cancer a vaccine-preventable disease [3, 4].

HPV is also the causal agent of genital warts, a widespread problem with a global annual incidence of 195 per 100 000 population [5]. Although genital warts are not life threatening, they are one of the most frequent sexually transmitted infections, resulting in negative quality of life consequences [6, 7].

Women living with HIV (WLWH) are disproportionately affected by HPV infection and cervical cancer, with HIV infection being an independent risk factor for cervical cancer [8, 9]. WLWH have a 47-53% prevalence of HPV infection, which is approximately double the prevalence among women without HIV (22-29%) [10, 11]. Compared to invasive cervical cancers (ICCs) in women without HIV, ICCs in WLWH have a higher prevalence of oncogenic HPV types other than HPV16 and 18, which appears to be due to higher rates of multiple HPV infection among WLWH [12]. Despite widespread screening programs in HIC, WLWH continue to experience higher and more rapid rates

of progression to high-grade cervical dysplasia and ICC than women without HIV. Among North American women, WLWH have an ICC incidence rate of 26 per 100 000 person-years, compared to 6 per 100 000 person-years in women without HIV [13]. WLWH are also more likely to experience larger and more recurrent warts; genital wart incidence was reported as 5.0 per 100 person-years in WLWH compared to 1.3 per 100 person-years in women without HIV [14].

HPV vaccines exist in bivalent, quadrivalent, and nonavalent formulations. These vaccines have shown a high degree of safety, immunogenicity, and efficacy in HIV-negative populations [15-27]. HPV vaccine safety and immunogenicity results within populations with HIV appear promising [28-30], with data from our cohort showing 94-99% seroconversion and improved peak geometric mean titres (GMTs) in participants with HIV virologic suppression compared to those not suppressed [31]. There has been a prior publication of HPV vaccine efficacy in persons living with HIV [32], but none to date of WLWH and none with cervical disease endpoints. This analysis assesses the 2-year efficacy of the quadrivalent HPV (qHPV) vaccine in a cohort of WLWH. As no immune correlate of protection for HPV has been established, efficacy findings are critical to better understand how the HPV vaccine performs in individuals with HIV. HPV vaccines are currently offered in HIV-endemic countries without HIV-specific efficacy data to support schedule recommendations for individuals with HIV. As the first report of infection and histological outcomes in WLWH post HPV vaccination, these findings will inform vaccine rollout for this population globally.

Methods

Study population

Girls and WLWH were recruited from 14 HIV clinics across Canada between 2008-2012, as described in a previous publication [31]. Eligibility included: aged 9 years or older, not pregnant, willing to avoid pregnancy during the vaccination series, and had to have a cervix. Recruited individuals were ineligible if they had received any HPV vaccine, had an allergy to vaccine components, were currently enrolled in a trial of an investigational drug or vaccine, or if a site investigator deemed their health to be exclusionary. Participants, or guardians, provided voluntary informed consent to participate.

Study Design

Participants were asked to attend 8 study visits: one screening visit (-3 months) and 7 study visits (month 0/2/6/7/12/18/24), and were to receive three doses of qHPV vaccine intramuscularly at month 0/2/6. Pelvic examination was performed on participants who were post-menarchal and sexually active. Cervical cytology and cervico-vaginal HPV DNA samples were collected at screening and at month 0/6/12/18/24. Cervical cytology samples were collected using ThinPrep® Pap Test and were classified by Bethesda Criteria at the British Columbia Cancer Agency Cervical Cancer Screening Laboratory. For HPV DNA detection, cervico-vaginal samples collected in PreservCyt® were processed and typed for 36 HPV genotypes by Linear array assay (Roche Molecular Systems) [33]. Participants were referred for colposcopies as per regional recommendations. Histological diagnoses were collected from pathology reports of

144 individuals who underwent colposcopy with cervical biopsy and/or endocervical
145 curettage.
146
147 **Statistical Methods**
148 In this efficacy analysis, newly acquired persistent HPV infection was defined as the
149 detection of the same qHPV type (i.e., HPV type protected against by the qHPV vaccine;
150 HPV6/11/16/18) in samples collected at two or more consecutive visits (>6 months apart)
151 or detection of qHPV at the last available visit [34].
152
153 The second endpoint was incident cervical intraepithelial neoplasia of grade 2 and higher
154 (CIN2+). Participants considered for this endpoint had to have normal baseline cytology.
155 A third endpoint was incident genital warts and participants had to have no genital warts
156 present at baseline to be considered for this endpoint. Duration of follow-up for the
157 endpoints varies due to the differing inclusion criteria.
158
159 Analyses were undertaken in three sub-populations. The per-protocol efficacy (PPE)
160 population included those who received all three doses of vaccine within 1 year and who
161 had at least one follow-up visit including pelvic examination after month 7 post initial
162 vaccination. Participants had to be naïve to the relevant qHPV type at baseline by
163 competitive Luminex immunoassay and Linear array assay (i.e., antibody and DNA
164 negative). Case counting for this population began at month 7. A naïve to relevant type
165 (NRT) population and an intention-to-treat (ITT) population were also considered.
166 Participants in the NRT population received at least one dose of vaccine, attended at least

one follow-up visit with pelvic examination after day 1, and were naïve to the relevant qHPV type at baseline. Participants included in the ITT group received at least one dose of vaccine and attended at least one follow-up visit with pelvic examination after day 1. Case counting began on day 1 for participants in the NRT and ITT analyses.

Due to the known safety and efficacy of the qHPV vaccine in the pre-licensure trials, it was unethical to perform a placebo-controlled study. However, comparisons were drawn between our cohort and a cohort of women without HIV to provide context for our results. The most suitable group for comparison was that of Muñoz et al., 2009 which had a similar median follow-up time of 2.2 years and age range of 24-45 years (median=35, n=1911) [18]. In order to improve similarity of our cohort to this comparator group, PPE, NRT, and ITT sub-populations for comparison were created in which participants from our cohort were excluded if they had a history of genital warts, history of cervical disease, or past cervical surgical procedure as these women would have been ineligible for the Muñoz et al. study. The comparator group utilized a composite endpoint of persistent qHPV, external genital disease, or cervical disease associated with qHPV types. Results for the same composite endpoint were procured within our vaccinated WLWH to assess differences. The definitions of these endpoints were consistent between studies.

Comparison was also made to unvaccinated WLWH from a previous study, the Canadian Women's HIV Study (CWHS) [10]. CWHS followed 750 WLWH in the pre-HPV vaccine era (1993-2002) and had the same median follow-up time of 2 years, a similar

median age of 33 (interquartile range [IQR]: 28-38), a similar ethnic makeup, and participants received their care at many of the same clinics across Canada [10].

Results

420 girls and women were enrolled in this national observational study. Of those enrolled, 279 women met inclusion criteria for at least one sub-population of this 2-year efficacy analysis; reasons for non-inclusion are described in Figure 1. Baseline characteristics of eligible participants are shown in Table 1. The median age was 39 years (IQR: 34-45, range: 13-66). Participants were ethnically mixed but predominantly Black (41.9%) and White (36.2%). The region of origin was predominantly Canada (50.5%), followed by Africa (33.3%). The median CD4 count at first vaccination was 500 cells/mm^3 (IQR: 380-682) and 69% of participants had HIV plasma viral loads <50 copies/mL. 266 (95.3%) received all three doses of vaccine, 7 (2.5%) received 2 doses, and 6 (2.2%) received 1 dose. At baseline, the most frequently detected HPV types were HPV16 (10.3%), HPV52 (9.1%), and HPV45 (7.1%). Prevalent HPV18 infection was only seen in 5.6% of participants. The vaccine was found to be safe and highly immunogenic within this population, as previously described [31].

Among women in the ITT group (Table 2), 11 cases of newly acquired persistent qHPV were observed in 477.7 person-years of follow-up (median follow-up 2 years, IQR: 1.6-2.1). The incidence rate of this endpoint was 2.3 per 100 person-years (95% confidence interval [CI]: 1.1-4.1). Six of the persistent qHPV infections were HPV18, three were

HPV6, one was HPV11, and one was HPV16. The incidence rate of genital warts was 2.3 per 100 person-years (95% CI: 1.2-4.1). No cases of qHPV-associated CIN2+ were seen in women with normal baseline cytology.

Within the NRT population, the incidence rate of newly acquired persistent qHPV was 1.1 per 100 person-years (95% CI: 0.3-2.5) and the incidence rate of genital warts was 2.1 per 100 person-years (95% CI: 1.0-3.9). All cases of persistent qHPV were due to HPV18. No cases of CIN2+ were observed.

Among 212 women eligible for the PPE population, the incidence rate of newly acquired persistent qHPV was 1.0 per 100 person-years (95% CI: 0.3-2.6). All four cases of persistent qHPV were due to HPV18. No cases of qHPV-associated CIN2+ developed among women with normal baseline cytology. There were, however, 2 cases of cytological HSIL, 1 atypical glandular cells (AGC), and 1 atypical squamous cells – cannot exclude HSIL (ASC-H) in women with normal baseline cytology. None of these abnormal cytology results were qHPV-associated. Within the PPE population, the incidence rate of genital warts was 1.0 per 100 person-years (95% CI: 0.3-2.5). Of the four genital wart cases, three were HPV6 DNA-positive at baseline and one had a history of warts and was HPV6 DNA-positive at the time of wart detection. As such, these newly clinically recognized warts were likely due to pre-existing infection.

Although there were too few events of vaccine failure within the PPE group to assess predictors in a statistically robust manner, some trends were observed (Table 3). The

236 eight cases had a median baseline CD4 count of 333 cells/mm^3 (IQR: 298-435), which
237 was lower than the median of 513 cells/mm^3 (IQR: 390-700) among women who had not
238 experienced vaccine failure. Similarly, the median CD4 nadir of those who experienced
239 vaccine failure (37 cells/mm^3, IQR: 32-283) was lower than the median CD4 nadir of
240 those who did not (240 cells/mm^3, IQR: 133-339). Among those who experienced
241 breakthrough persistent qHPV, all of which were HPV18, the median log peak HPV18
242 geometric mean titre (GMT) was 5.95 (IQR: 4.3-6.3), which was similar to the median of
243 5.87 (IQR: 4.8-6.7) for those who did not experience breakthrough.
244
245 It was notable that all four cases of breakthrough persistent qHPV in the PPE group were
246 HPV18. In the NRT group, the same four cases of HPV18 were seen as well as one
247 additional case of HPV18. As this is a statistically unlikely situation given the higher
248 prevalence of HPV16 and 6 in the general population, this finding was further explored.
249 This finding was not due to laboratory contamination as the samples were collected over
250 the span of one year, did not undergo HPV DNA testing concurrently, and all negative
251 controls during this year tested negative. Screening and baseline samples from these
252 participants were re-tested with an HPV18-specific real time PCR assay to determine if
253 these individuals were incorrectly classified as naïve to HPV18 at study initiation [35].
254 The real time assay revealed that the one individual who was only in the NRT group was
255 infected with HPV18 at screening and thereby did not represent vaccine failure. The
256 sample contained a very low HPV18 copy number, which explains why it was previously
257 negative via the less sensitive Linear array assay. All PPE cases remained classified as
258 naïve to HPV18 at baseline with the real time PCR assay (data not shown).

Of the four HPV18 cases, one was a persistent infection present at two consecutive study visits. In the remaining samples, HPV18 was only present in the last available sample.

Comparison to the Muñoz et al. cohort of women without HIV [18] showed that the rates of the composite endpoint (i.e., vaccine failure) were greater in our cohort of WLWH for the PPE group compared to the HIV-negative vaccinated PPE group (1.2 versus 0.1 per 100 person-years, rate ratio: 11.7 [95% CI: 2.6-52.1]), while not significantly greater when comparing the NRT or ITT groups (NRT rate ratio: 4.1, ITT rate ratio: 1.1) (Table 4). In fact, the composite endpoint rates within our groups of vaccinated WLWH were not different from the HIV-negative placebo group rates (PPE rate ratio: 0.8; NRT rate ratio: 1.0; ITT rate ratio: 0.8).

We also compared the incidence rates of persistent qHPV, CIN2+, and genital warts to a cohort of unvaccinated WLWH from the CWHS conducted in the pre-HPV vaccine era (Table 5) [10]. The rate of persistent qHPV is substantially lower among vaccinated WLWH compared to the historical unvaccinated group (2.3 versus 6.0 per 100 person-years). However, the rates of genital warts and CIN2+ do not differ as greatly (2.3 versus 2.9 per 100 person-years and 0 versus 1 per 100 person-years, respectively).

Discussion

The fact that our WLWH experienced rates of persistent qHPV and qHPV-related disease similar to those of an HIV-negative placebo group from the literature [18] suggests that WLWH may be at higher risk for vaccine failure than their HIV-negative counterparts. However, the rate of newly acquired persistent qHPV was significantly less than the rate seen in unvaccinated WLWH in the literature [10], which suggests that although protection is not as complete as that seen in women without HIV, an important benefit appears to be present.

Overall rates of vaccine failure were low within this cohort of WLWH. The fact that three out of four HPV18 breakthrough infections were cases in which the infection was present at the last available sample, and not persistent between two study visits, does not diminish the relevance of our findings because the definition of breakthrough persistent qHPV infection is consistent with other studies of HPV vaccine efficacy. The lack of any CIN2+ diagnoses thus far is encouraging but not a surprising finding at two years of follow-up as CIN2+ usually requires 7-10 years to develop in women without HIV [36]; however, this remains a promising finding, as median time to CIN2+ diagnosis has been reported to be as short as three years in women without HIV [37]. Further follow-up is underway to assess longer-term efficacy of the vaccine within this cohort.

The disparities noted between the median baseline CD4 counts and CD4 nadirs of all PPE cases and non-cases suggest that present and historical immune dysfunction may contribute to breakthrough HPV infection and disease as a whole, not solely to HPV18

304 breakthrough. Higher case numbers are required to properly elucidate this relationship.
305 The fact that a higher incidence of HPV-associated disease is seen in WLWH who have
306 CD4 counts below 350 cells/μL supports the idea that impaired immune functionality
307 caused by HIV may play a role in HPV persistence and disease [38] and that HPV-
308 specific CD4 responses to the vaccine may be deficient in women with breakthrough
309 infection and disease despite overall good immunogenicity in this cohort [31]. Future
310 studies assessing CD4-induced vaccine responses in WLWH would provide valuable
311 insight. Importantly, comparisons between groups of women who experienced vaccine
312 failure and those who did not may evolve as further vaccine failure may occur in time.
313
314 **Strengths and Limitations**
315
316 To our knowledge, this study is the first report of HPV vaccine efficacy against cervical
317 infection and disease in WLWH, providing valuable insights towards prevention of HPV-
318 associated disease in this population. Study limitations include moderate cohort size with
319 relatively short follow-up time of two years, which affected our ability to produce highly
320 precise confidence intervals. This cohort continues to be followed and future reporting on
321 longer follow-up is forthcoming. Due to the ethical limitation of not using a placebo
322 group, our comparisons utilize comparable published data from an HIV-negative
323 vaccinated cohort [18] and a historical group of WLWH [10]. Partner deposition of HPV
324 could be responsible for the detection of some HPV cases. Recent literature suggests that
325 only approximately 14% of HPV DNA detected in a cohort of Canadian women is due to
326 recent vaginal sex [39].

Conclusions

Given the relatively low rate of vaccine failure within the first two years of follow-up, paired with a good safety and immunogenicity profile, the HPV vaccine should continue to be offered to a wide age range of WLWH. It is, however, important to recognize that WLWH appear to be at higher risk than women without HIV for acquiring persistent qHPV-related infection and disease despite vaccination against HPV. As a result, regular cervical screening remains important in vaccinated WLWH. Even though the protection may not be as complete, the rate of persistent qHPV is greatly diminished in vaccinated compared to unvaccinated WLWH. Longer-term follow-up will better inform vaccine schedule recommendations for this population.

Funding

This work was supported by the Canadian Institutes for Health Research (CIHR) [funding reference number: MOP 136784]; CIHR Canadian HIV Trials Network (CTN 236); Réseau FRSQ SIDA-MI supported quality control of the Linear array; Chair in Biostatistics from the Ontario HIV Treatment Network to JR; Chair in Clinical Management and Aging from the Ontario HIV Treatment Network to SW; and in-kind contribution from Merck Canada Inc. The opinions expressed in this paper are those of the authors and do not necessarily represent those of Merck Canada Inc.

Acknowledgements

The authors would like to acknowledge the CTN 236 HPV in HIV Study Team, in alphabetical order: Ariane Alimenti, MD (University of British Columbia), Arezou Azampanah, MSc (Women's Health Research Institute), Ari Bitnun, MD (University of Toronto), Sandra Blitz, MSc (University Health Network), Jason Brophy, MD (University of Ottawa), Jan Christilaw, MD (University of British Columbia), Andrew Coldman, PhD (British Columbia Cancer Agency), Simon Dobson, MD (Vaccine Evaluation Centre), Catherine Hankins, MD, PhD (Amsterdam Institute for Global Health and Development), Christos Karatzios, MD (McGill University Health Centre), Mel Krajden, MD (British Columbia Centre for Disease Control), Normand Lapointe, MD (CHU Sainte Justine), Jessica McAlpine, MD (University of British Columbia), Dianne Miller, MD (University of British Columbia), Erin Moses, RN, MPH (Women's Health Research Institute), Dirk van Niekerk, MD (British Columbia Cancer Agency), Gina Ogilvie, MD, DrPH (University of British Columbia), Neora Pick, MD (University of British Columbia), Lindy Samson, MD (University of Ottawa), Julie van Schalkwyk, MD (University of British Columbia), David Scheifele, MD (Vaccine Evaluation Centre), Joel Singer, PhD (CIHR Clinical Trials Network), Sarah Stone, MD (British Columbia Centre for Excellence in HIV/AIDS), Gavin Stuart, MD (University of British Columbia), Marcie Summers (Positive Women's Network), Laura Vicol, MN, NP (University of British Columbia), and Melissa Watt (Women's Health Research Institute). The authors wish to thank all of the additional clinicians and research staff for their important

372 contributions to participant enrollment and study visits. We would also like to thank the
373 participants without whom this research would not be possible.
374

375 **Disclosure of Interests**

376 Dr. Lee has received honoraria from Merck Canada Inc.
377 Dr. Raboud is a co-investigator on three projects outside the submitted work, with in-kind
378 contributions or financial support from Merck and Gilead Sciences.
379 Dr. Coutlée has received grants for research projects from Roche Diagnostics, Becton
380 Dickenson, and Merck, Sharp, and Dome, honoraria for presentations from Merck, Sharp,
381 and Dome and Roche Diagnostics, and has participated in an expert group by Merck,
382 Sharp, and Dome, outside the submitted work.
383 Dr. Walmsley has received grants, personal fees and non-financial support from Merck
384 Canada Inc., ViiV Healthcare, Gilead, AbbVie, Janssen and BMS for participation on
385 advisory boards, presentations, meetings, studies, workshops and symposia for each,
386 outside the submitted work.
387 Dr. Loutfy has received grant and honoraria funding from Merck Canada Inc., ViiV
388 Healthcare, and Gilead, unrelated to the submitted work.
389 Dr. Trottier has received grants from ViiV Healthcare, Gilead, GlaxoSmithKline, and
390 Merck, outside the submitted work.
391 Dr. Smaill received grant and honoraria funding from Merck Canada Inc., ViiV
392 Healthcare, and Gilead, unrelated to the submitted work.

Dr. Klein has received funding for investigator-initiated research from ViiV and Merck, unrelated to this work, and honoraria for participation in advisory boards from Merck, ViiV, and BMS.

Dr. Harris has received grants, paid to the institution, from the Canadian Institutes of Health Research (CIHR) and honoraria for consultancy and/or speaking engagements from Gilead Sciences Canada Inc., Merck Canada Inc., and ViiV Healthcare, outside the submitted work.

Dr. Wobeser has received grants, personal fees, and non-financial support from Merck Canada Inc., ViiV Healthcare, Gilead, AbbVie, and Janssen for participation on advisory boards, presentations, meetings, and studies for each, outside of the submitted work.

Dr. Money has received grants from GSK and Merck Canada Inc. for conducting sponsored vaccine trials. She also reports grants from Novartis and Sanofi for conducting sponsored vaccine trials in an unrelated area. She has received personal fees for symposium participation from Merck Canada Inc., outside the submitted work.

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.

References

1. Ferlay J, Ervik M, Dikshit R, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancerbase No. 11. Lyon, **2013**.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global Cancer Statistics, 2012. CA Cancer J Clin, **2015**; 65(2).
3. Koutsky LA, Harper DM. Chapter 13: Current findings from prophylactic HPV vaccine trials. Vaccine, **2006**; 24: S114-S21.
4. IARC. Human Papillomaviruses - IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Geneva: World Health Organization, **2007**.
5. Patel H, Wagner M, Singhal P, Kothari S. Systematic review of the incidence and prevalence of genital warts. BMC Infect Dis, **2013**; 13(1): 1-14.
6. von Krogh G, Lacey CJN, Gross G, Barrasso R, Schneider A. European course on HPV associated pathology: guidelines for primary care physicians for the diagnosis and management of anogenital warts. Sex Transm Infect, **2000**; 76(3): 162-8.
7. Maw RD, Reitano M, Roy M. An international survey of patients with genital warts: perceptions regarding treatment and impact on lifestyle. Int J STD AIDS, **1998**; 9.
8. Ferenczy A, Coutlee F, Franco E, Hankins C. Human papillomavirus and HIV coinfection and the risk of neoplasias of the lower genital tract: a review of recent developments. CMAJ, **2003**; 169(5): 431-4.
9. Wright TC, Ellerbrock TV, Chiasson MA, Devanter NV, Sun X-W. Cervical Intraepithelial Neoplasia in Women Infected With Human Immunodeficiency Virus: Prevalence, Risk Factors, and Validity of Papanicolaou Smears. Obstet Gynecol, **1994**; 84(4, Part 1): 591-7.
10. Blitz S, Baxter J, Raboud J, et al. Evaluation of HIV and highly active antiretroviral therapy on the natural history of human papillomavirus infection and cervical cytopathologic findings in HIV-positive and high-risk HIV-negative women. J Infect Dis, **2013**; 208(3): 454.
11. Massad LS, Xie X, Burk R, et al. Long-term cumulative detection of human papillomavirus among HIV seropositive women. AIDS, **2014**; 28(17): 2601-8.
12. Clifford GM, de Vuyst H, Tenet V, Plummer M, Tully S, Franceschi S. Effect of HIV Infection on Human Papillomavirus Types Causing Invasive Cervical Cancer in Africa. JAIDS, **2016**; 73(3): 332-9.
13. Abraham AG, D'Souza G, Jing YZ, et al. Invasive Cervical Cancer Risk Among HIV-Infected Women: A North American Multicohort Collaboration Prospective Study. JAIDS, **2013**; 62(4): 405-13.
14. Massad LS, Silverberg MJ, Springer G, et al. Effect of antiretroviral therapy on the incidence of genital warts and vulvar neoplasia among women with the human immunodeficiency virus. Am J Obstet Gynecol, **2004**; 190(5): 1241-8.
15. Villa LL, Costa RLR, Petta CA, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in

young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol, **2005**; 6(5): 271-8.
16. Villa LL, Perez G, Kjaer SK, et al. Quadrivalent Vaccine against Human Papillomavirus to Prevent High-Grade Cervical Lesions. N Engl J Med, **2007**; 356(19): 1915-27.
17. Joura EA, Kjaer SK, Wheeler CM, et al. HPV antibody levels and clinical efficacy following administration of a prophylactic quadrivalent HPV vaccine. Vaccine, **2008**; 26(52): 6844-51.
18. Muñoz N, Manalastas Jr R, Pitisuttithum P, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24–45 years: a randomised, double-blind trial. Lancet, **2009**; 373(9679): 1949-57.
19. Castellsagué X, Muñoz N, Pitisuttithum P, et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age. Br J Cancer, **2011**; 105(1): 28-37.
20. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent Vaccine against Human Papillomavirus to Prevent Anogenital Diseases. N Eng J Med, **2007**; 356(19): 1928-43.
21. Luna J, Plata M, Gonzalez M, et al. Long-term follow-up observation of the safety, immunogenicity, and effectiveness of Gardasil™ in adult women. PloS One, **2013**; 8(12): e83431.
22. Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. N Engl J Med, **2011**; 364.
23. Nygård M, Saah A, Munk C, et al. Evaluation of the Long-Term Anti-Human Papillomavirus 6 (HPV6), 11, 16, and 18 Immune Responses Generated by the Quadrivalent HPV Vaccine. Clin Vaccine Immunol, **2015**; 22(8): 943-8.
24. Paavonen J, Naud P, Salmerón J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet, **2009**; 374(9686): 301-14.
25. Skinner SR, Szarewski A, Romanowski B, et al. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. Lancet, **2014**; 384(9961): 2213-27.
26. Koutsky LA, Ault KA, Wheeler CM, et al. A Controlled Trial of a Human Papillomavirus Type 16 Vaccine. N Engl J Med, **2002**; 347(21): 1645-51.
27. Rowhani-Rahbar A, Mao C, Hughes JP, et al. Longer term efficacy of a prophylactic monovalent human papillomavirus type 16 vaccine. Vaccine, **2009**; 27(41): 5612-9.
28. Kahn JA, Xu J, Kapogiannis BG, et al. Immunogenicity and safety of the human papillomavirus 6, 11, 16, 18 vaccine in HIV-infected young women. Clin Infect Dis, **2013**; 57(5): 735-44.

29. Kojic EM, Kang M, Cespedes MS, et al. Immunogenicity and safety of the quadrivalent human papillomavirus vaccine in HIV-1-infected women. Clin Infect Dis, **2014**; 59(1): 127-35.
30. Giacomet V, Penagini F, Trabattoni D, et al. Safety and immunogenicity of a quadrivalent human papillomavirus vaccine in HIV-infected and HIV-negative adolescents and young adults. Vaccine, **2014**; 32(43): 5657.
31. Money DM, Moses E, Blitz S, et al. HIV viral suppression results in higher antibody responses in HIV-positive women vaccinated with the quadrivalent human papillomavirus vaccine. Vaccine, **2016**; 34(40): 4799-806.
32. Wilkin TJ, Chen H, Cespedes MS, et al. A randomized, placebo-controlled trial of the quadrivalent HPV vaccine in HIV-infected adults age 27 years or older: AIDS Clinical Trials Group protocol A5298. Clin Infect Dis, **2018**.
33. Coutlée F, Rouleau D, Petignat P, et al. Enhanced Detection and Typing of Human Papillomavirus (HPV) DNA in Anogenital Samples with PGMY Primers and the Linear Array HPV Genotyping Test. J Clin Microbiol, **2006**; 44(6): 1998-2006.
34. Lowy DR, Herrero R, Hildesheim A, Participants in the INCIwoPEfPHPVVT. Primary endpoints for future prophylactic human papillomavirus vaccine trials: towards infection and immunobridging. Lancet Oncol, **2015**; 16(5): e226-e33.
35. Ramanakumar AV, Goncalves O, Richardson H, et al. Human papillomavirus (HPV) types 16, 18, 31, 45 DNA loads and HPV-16 integration in persistent and transient infections in young women. BMC Infect Dis, **2010**; 10(1): 326-.
36. Schiffman M, Kjaer SK. Chapter 2: Natural history of anogenital human papillomavirus infection and neoplasia. J Natl Cancer Inst Monogr, **2003**; 2003(31): 14-9.
37. Woodman CBJ, Collins S, Winter H, et al. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. Lancet, **2001**; 357(9271): 1831-6.
38. Biggar RJ, Chaturvedi AK, Goedert JJ, Engels EA, Study HACM, For the HIVACMS. AIDS-Related Cancer and Severity of Immunosuppression in Persons With AIDS. J Natl Cancer Inst, **2007**; 99(12): 962-72.
39. Franco EL, Burchell AN, Guenoun J, et al. Estimating HPV DNA Deposition Between Sexual Partners Using HPV Concordance, Y Chromosome DNA Detection, and Self-reported Sexual Behaviors. J Infect Dis, **2017**; 216(10): 1210.

546 **Tables**

547 Table 1: Study Population Characteristics (n=279)

548

Characteristic	N (%) or Median (IQR)
Age	39 (34-45)
Ethnicity	
Asian	15 (5.4%)
Black	117 (41.9%)
Hispanic	4 (1.4%)
Indigenous	39 (14.0%)
White	101 (36.2%)
Other	3 (1.1%)
Region of origin	
Africa	93 (33.3%)
Asia	13 (4.7%)
Canada	141 (50.5%)
Caribbean	19 (6.8%)
Central America	4 (1.4%)
Europe	5 (1.8%)
South America	4 (1.4%)
Total lifetime sexual partners	6 (3-12)
Years since HIV diagnosis	8 (4-12)
Baseline CD4 count (cells/mm^3)	500 (380-682)
CD4 nadir (cells/mm^3)	230 (118-339)
HIV viral load suppression (VL<50 copies/mL)	192 (68.8%)
Unknown	9 (3.2%)
ARV regimen status	
PI-based	135 (48.4%)
NNRTI-based	75 (26.9%)
Not yet started	17 (6.1%)
Previously on ARVs	10 (3.6%)
Other	30 (10.8%)
Unknown	11 (3.9%)
Baseline cytology	
Normal	226 (81.0%)
ASCUS	9 (3.2%)
LSIL	25 (9.0%)
ASC-H	1 (0.4%)
HSIL	9 (3.2%)
No result	9 (3.2%)
Number of vaccine doses	
3	266 (95.3%)
2	7 (2.5%)

1	6 (2.2%)

Abbreviations: IQR, interquartile range; ARV, antiretroviral; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; ASC-H, atypical squamous cells – cannot exclude HSIL; HSIL, high-grade squamous intraepithelial lesion.

572 Table 2: Incidence Rates of Study Endpoints within PPE, NRT, and ITT Populations

573

	N	Cases	Person-years	Rate (95% CI)
PPE population				
Breakthrough persistent qHPV	212	4	396.5	1.0 (0.3-2.6)
Genital warts	211	4	403.0	1.0 (0.3-2.5)
CIN2+	177	0	334.6	0 (0.0-1.1)
NRT population				
Breakthrough persistent qHPV	260	5	464.6	1.1 (0.3-2.5)
Genital warts	258	10	467.1	2.1 (1.0-3.9)
CIN2+	210	0	375.9	0 (0.0-1.0)
ITT population				
Breakthrough persistent qHPV	268	11	477.7	2.3 (1.1-4.1)
Genital warts	264	11	476.7	2.3 (1.2-4.1)
CIN2+	217	0	387.1	0 (0.0-0.9)

574

575 Abbreviations: CI, confidence interval; qHPV, quadrivalent HPV (HPV6/11/16/18);

576 CIN2+, cervical intraepithelial lesion of grade 2 or higher; PPE, per-protocol efficacy;

577 NRT, naïve to relevant type; ITT, intention-to-treat.

578

579

580

581

582

583 Table 3: PPE Vaccine Failure Listing

584

Case Type	Baseline Age	Baseline CD4 Count (cells/mm^3)	CD4 Nadir (cells/mm^3)	Screening HIV Viral Load (copies/mL)	Baseline HIV Viral Load (copies/mL)	Time to Infection or Disease/ Duration of Follow-Up (years)	Log Peak HPV 18 GMT
qHPV	20	430	400	425	20 027	2.0	5.37
qHPV	44	292	32	<50	<50	1.6	5.86
qHPV	49	320	33	<50	<50	1.8	6.95
qHPV	30	1570	767	<50	<50	2.0	6.03
Wart	47	130	40	<50	96 952	1.6	NA
Wart	42	450	30	<50	NA	0.6	NA
Wart	42	346	244	<50	<50	0.6	NA
Wart	27	300	30	<50	71	1.5	NA
Median of Cases	42	333	37			1.6	5.95
Median of Non-Cases	39	513	240			2.0	5.87

585

586 Abbreviations: GMT, geometric mean titre; qHPV, quadrivalent HPV (HPV6/11/16/18).

587 Table 4: Comparison of Composite Endpoint Rates in WLWH Versus Women Without HIV

	Muñoz et al., 2009 Vaccinated HIV-negative			Muñoz et al., 2009 Placebo HIV-negative			Present study Vaccinated WLWH			Vaccinated WLWH vs Vaccinated HIV-	Vaccinated WLWH vs Placebo HIV-
	n	Cases of composite endpoint	Rate (per 100 person-years)	n	Cases of composite endpoint	Rate (per 100 person-years)	n	Cases of composite endpoint	Rate (per 100 person-years)	Rate ratio (95% CI)	Rate ratio (95% CI)
PPE	1615	4	0.1 (0.02-0.03)	1607	41	1.5 (1.1-2.0)	137	3	1.2 (0.2-3.4)	11.7 (2.6-52.1)	0.8 (0.2-2.5)
NRT	1841	20	0.5 (0.3-0.8)	1833	77	2.0 (1.6-2.5)	163	6	2.0 (0.7-4.5)	4.1 (1.6-10.2)	1.0 (0.4-2.3)
ITT	1886	108	2.7 (2.2-3.3)	1883	154	3.9 (3.3-4.6)	167	9	3.0 (1.4-5.7)	1.1 (0.6-2.2)	0.8 (0.4-1.5)

588

589

590 Abbreviations: PPE, per-protocol efficacy; NRT, naïve to relevant type; ITT, intention-to-treat; CI, confidence interval; WLWH,

591 women living with HIV.

592

593

594

595

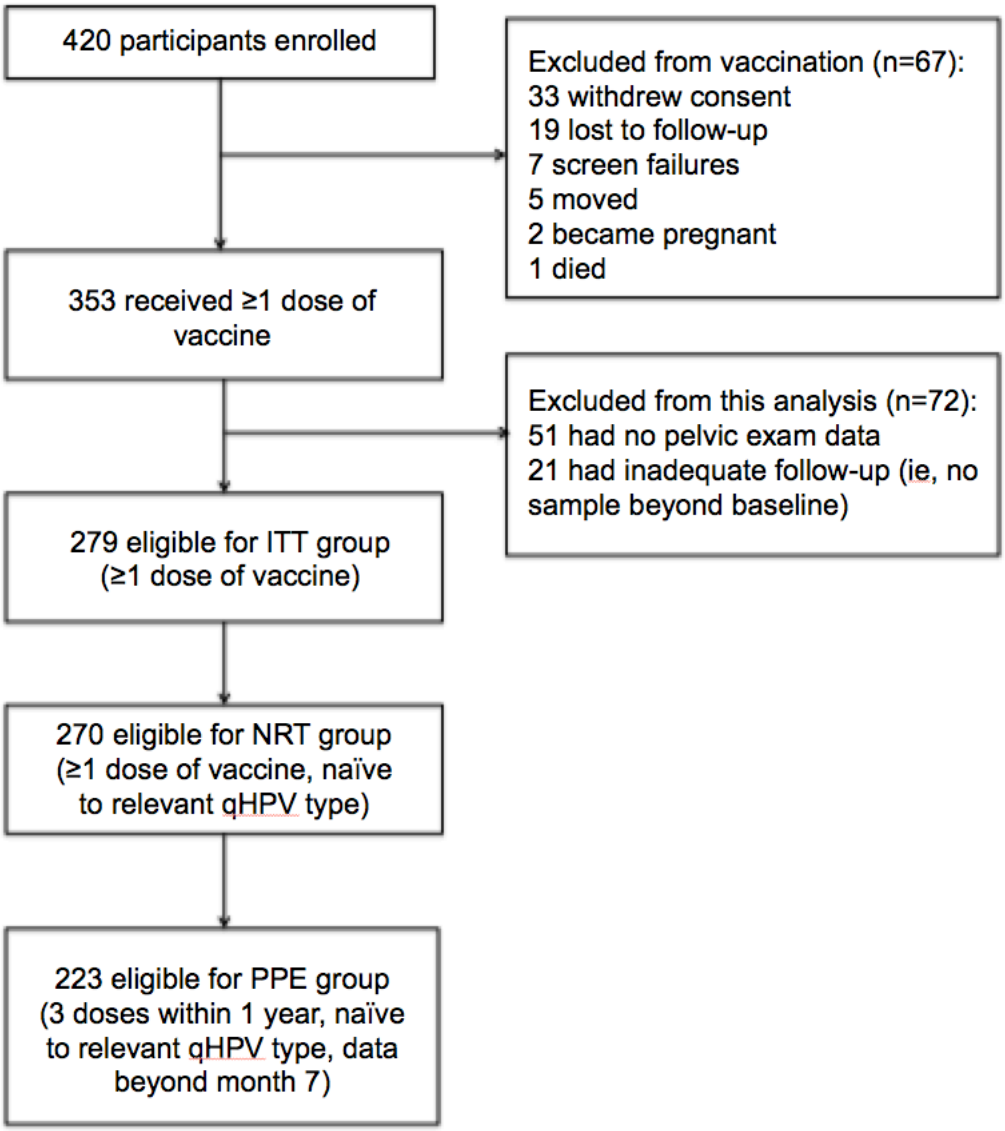
Table 5: Comparison to Unvaccinated Historical WLWH

	Unvaccinated Historical WLWH (Canadian Women's HIV Study)	Vaccinated WLWH (Present study)
Endpoint	**Rate per 100 person-years (95% CI)**	**Rate per 100 person-years (95% CI)**
Persistent qHPV	6.0 (4.6-7.7)	2.3 (1.1-4.1)
Genital warts	2.9 (2.1-3.9)	2.3 (1.2-4.1)
CIN2+	1.0 (0.5-1.9)	0 (0.0-0.9)

Abbreviations: WLWH, women living with HIV; CI, confidence interval; qHPV, quadrivalent HPV (HPV6/11/16/18); CIN2+, cervical intraepithelial lesion of grade 2 or higher.

613 Figure 1: Flowchart of Study Participants.

614



615

616 Abbreviations: ITT, intention-to-treat; NRT, naïve to relevant type; PPE, per-protocol

617 efficacy; qHPV, quadrivalent HPV (HPV6/11/16/18).

618