Impact of Quadrivalent HPV Vaccine Dose Spacing on Immunologic Response in Women Living with HIV

Authors: Elisabeth McClymont [a], Gina Ogilvie [b,c], Arianne Albert [c], Angela Johnston [d], Janet Raboud [e,f], Sharon Walmsley [e,f], Nancy Lipsky [c], Mona Loutfy [g], Sylvie Trottier [h], Fiona Smaill [i], Mark H. Yudin [g,j], Marina B. Klein [k], Marianne Harris [l], Wendy Wobeser [m], Ari Bitnun [n], Fatima Kakkar [o,p], Lindy Samson [q], Jason Brophy [r], Christos Karatzios [s,t], 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] School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada
[c] Women's Health Research Institute, Vancouver, BC, Canada
[d] Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada
[e] Toronto General Hospital Research Institute, University Health Network, University of Toronto, Toronto, ON, Canada
[f] Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada
[g] Women's College Research Institute, Women's College Hospital, 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] Department of Obstetrics and Gynecology, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada
[k] McGill University Health Centre, Montreal, QC, Canada
[l] British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada
[m] Departments of Public Health and Biomedical & Molecular Sciences, Queen's University, Kingston, ON, Canada
[n] Hospital for Sick Children, Department of Paediatrics, University of Toronto, Toronto, ON, Canada
[o] Department of Pediatrics, Faculty of Medicine, Université de Montréal, Montreal, QC, Canada
[p] Centre Maternel et Infantile sur le SIDA, CHU Sainte-Justine, Montreal, QC, Canada
[q] Department of Paediatrics, University of Ottawa, Ottawa, ON, Canada
[r] Department of Pediatrics, Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, ON, Canada
[s] Department of Paediatrics, Centre Hospitalier Universitaire Sainte-Justine, Université de Montréal, Montreal, QC, Canada
[t] Department of Pediatrics, Montreal Children's Hospital, McGill University Health Centre, Montreal, QC, Canada

This is the peer reviewed version of the following article: McClymont E, Ogilvie G, Albert A, Johnston A, Raboud J, Walmsley S, Lipsky N, Loutfy M, Trottier S, Smaill F, Yudin MH, Klein MB, Harris M, Wobeser W, Bitnun A, Kakkar F, Samson L, Brophy J, Karatzios C, Money D. Impact of quadrivalent HPV vaccine dose spacing on immunologic response in women living with HIV. Vaccine. 2020 Mar 30;38(15):3073-3078, which has been published in final form at doi: 10.1016/j.vaccine.2020.02.075.

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.

Running title: HPV Vaccine Dose Spacing in Women Living with HIV

Keywords: HPV vaccine, HIV, HPV, women

Word count: 1955 (abstract: 150)

Abstract

HPV vaccination schedules have changed as evidence has supported reduced dosing and extended intervals. Women living with HIV (WLWH) represent an important population with no data on alternative dosing.

Girls and WLWH received quadrivalent HPV (qHPV) vaccine in a pan-Canadian study of immunogenicity and efficacy. Serology was performed at months 0/2/7/12/18/24. Medical and sexual history was collected throughout. Linear regression was used to determine if spacing of doses was associated with peak antibody titer.

Multivariable analyses demonstrated significant relationships between peak antibody titer and time to blood draw post last vaccine dose, naivety to the relevant HPV type, and HIV viral load for all qHPV types. There was a significant relationship between peak HPV16/18 antibody titer and age.

Taking age, time to serology, CD4 cell count, CD4 nadir, HIV viral load, and HPV naivety into account, spacing of the three qHPV vaccine doses did not significantly impact peak antibody titers.

Background

Human papillomavirus vaccines are safe, immunogenic, and effective [1]. Initial dose schedules for quadrivalent, bivalent, and nonavalent formulations recommended three doses administered at months zero, one or two, and six [2]. However, more recent data have shown that young individuals who receive only two doses, and perhaps one dose, develop non-inferior peak antibody titers and may be adequately protected against persistent HPV infection and HPV-associated disease [3, 4]. Additionally, studies have shown that expanding the time frame of the three-dose schedule or delaying the second or third dose results in non-inferior immune responses in immunocompetent populations [5-8]. Reduced-dose schedules can greatly expand the financial feasibility of HPV vaccination globally and will help reach the global target of cervical cancer elimination [9].

Given the global goal of cervical cancer elimination, consideration of all female populations is critical. A group of particular importance in achieving this goal is women living with HIV (WLWH). WLWH have higher rates of persistent HPV infection, as well as an increased rate of HPV-associated disease [10-12]. In addition, countries with high rates of HIV also frequently have low rates of cervical cancer screening, and therefore are in the greatest need of simple, affordable vaccine schedules. The quadrivalent HPV (qHPV) vaccine has been shown to be safe, immunogenic, and efficacious in WLWH to date, with the greatest immune response seen in WLWH with undetectable HIV viral loads [13, 14]. However, to our knowledge, no study to date has evaluated the effect of qHPV vaccine dose spacing in this important population. In this study, we assess the effect of differential dose spacing of the qHPV vaccine on immunogenicity in WLWH.

Methods

Individuals aged nine and greater with a uterine cervix were recruited from 14 clinics serving WLWH across Canada between 2008-2012. The primary objective was to assess immunogenicity of the qHPV vaccine. The study population and methods of enrolment have been previously described [14]. Participants provided informed consent and were scheduled to receive three doses of qHPV vaccine intramuscularly at month 0/2/6. Serology was performed at month 0/2/7/12/18/24 by cLIA assay at Merck Research Laboratories.

The objective of this analysis was to determine if the spacing of qHPV vaccine doses had an impact on the peak antibody titer achieved in WLWH. Peak antibody titer was defined as the highest anti-HPV antibody titer achieved in a participant, for each HPV type, post-vaccination. Peak titer was chosen as an endpoint as it is a measure of maximal vaccine response and is associated with protection against disease endpoints [15]. Peak antibody titer was natural log transformed prior to analysis. Participants were divided into six groups based on vaccine spacing: one dose, two doses, three doses within seven months, three doses within seven months to one year, three doses within one to two years, and three doses over more than two years. We used Chi squared tests for trend for categorical variables and Spearman's rank correlation for continuous variables to assess differences in participant characteristics between vaccine spacing categories. Univariable and multivariable linear regression was performed for each qHPV type to examine if the spacing of the vaccine doses impacted the peak log titer for each HPV type. Linear regression models included potential confounders: age at first dose, time to blood draw

following last dose, CD4 count and HIV viral load at first vaccine dose, CD4 nadir, and naivety to the HPV type. We also ran a sensitivity analysis excluding participants aged <14 years.

Results

The participants who received one dose (n=6), two doses (n=4), and three doses over greater than two years (n=5) were removed from analysis due to low numbers. Participants who did not have serology performed after their last dose of vaccine were also removed due to the inability to assess the endpoint of interest (n=31). After these exclusions, 307 participants were eligible for analysis (Table 1). The median age was 36 years (IQR: 26-44). Participants were predominantly of Black (47%) and White (32%) ethnicity. Four percent of participants had CD4 counts below 200 cells/mm^3 at baseline (time of first vaccination) and 50% had CD4 counts above 500 cells/mm^3. Sixty-six percent of participants had HIV plasma viral loads <50 copies/ml at baseline. Sixty-five percent of participants were naïve to HPV16 at baseline and median peak HPV16 log titer among all participants was 7.7 (IQR: 6.9-8.4).

Two hundred and twenty-nine participants received three doses of vaccine within seven months, 56 received three doses within seven months to one year, and 22 received three doses within one to two years. Variables of interest were not significantly different between spacing categories (Table 1) with the exception of baseline CD4 count, naivety to HPV11, and time to blood draw post last vaccine dose. CD4 counts and rates of naivety to HPV11 decreased in the groups as the vaccine spacing increased. There was a similar but not significant trend for HPV16 naivety but no clear trend in HPV6 and 18.

158 The time to blood draw post last dose was significantly greater as the vaccine spacing
159 increased.

160 Univariable linear regression results suggested that HIV viral load detectability
161 and time to blood draw were significantly associated with peak antibody titer for all
162 qHPV types (Table 2). Peak antibody titers were 41-64% lower on average, depending on
163 qHPV type, in participants with detectable HIV viral loads, compared to those with
164 undetectable HIV viral loads. As time between last vaccine dose and blood draw for
165 serology increased, peak antibody response decreased, as expected based on immune titer
166 dynamics. For all qHPV types aside from 16, previously exposure to the relevant HPV
167 type was associated with 60-98% higher peak antibody titers, depending on qHPV type.
168 The same trend was present for HPV16 although it did not reach significance. Higher
169 baseline CD4 count was significantly associated with higher peak antibody titers for
170 HPV16 and 18. Additionally, older age was associated with lower peak antibody titers for
171 HPV16 only. Wider dose spacing was associated with lower peak antibody titers for
172 HPV18; participants who received all doses within 7 months to 1 year had non-
173 significantly higher peak antibody titers but participants who received all doses within 1
174 to 2 years had significantly lower peak antibody titers.

175 Multivariable linear regression yielded a significant relationship for all qHPV
176 types between peak antibody titer and HIV viral load, naivety to the relevant HPV type,
177 and time to blood draw (Table 2). Of note, there were no significant associations between
178 peak antibody titers and spacing of vaccine doses in multivariable analysis. Participants
179 with detectable HIV viral loads had peak antibody titers that were 39-64% lower on
180 average, depending on qHPV type. Participants who were previously exposed to the

relevant HPV type had peak antibody titers that were 44-77% higher on average, depending on qHPV type, compared to naïve participants. As time between last vaccine dose and blood draw for serology increased, peak antibody response decreased. There was also a significant relationship between peak antibody titer and age, but only for HPV16 and 18, in which lower age was associated with higher peak antibody response.

A sensitivity analysis excluded 33 girls aged ≤13 to assess the impact of age in the non-pediatric subset of the cohort. Girls aged ≤13 were not analyzed separately due to low numbers and lack of diversity of dosing schedules (31 girls had all doses within seven months and two girls had all doses within seven months to one year). After removing girls aged ≤13, the median age was 37 (IQR: 31-44, n=274). The proportion of all other characteristics described in Table 1 did not significantly change. Multivariable linear regression of this non-pediatric subset demonstrated a significant relationship between peak antibody titer and time to blood draw, naivety to the relevant HPV type, and HIV viral load for all qHPV types, as it had for the full population. Again, there was no significant association between peak antibody titer and spacing of vaccine doses. There remained a significant relationship between peak antibody titer and age, only for HPV18.

Discussion

Of most importance to this analysis, vaccine dose spacing did not appear to be associated with peak antibody response in multivariable analyses for all qHPV types. Although peak log titers do appear to decrease slightly in median value as doses become more widely spaced, particularly for HPV16 and 18 (Table 1), the difference is not

significant and can be accounted for by other variables in the models. The variables that did reach significance in our models are much more important to achieving a high antibody level in WLWH. Assay variability for the cLIA ranges based on HPV type from 16-23% relative standard deviation [16], such that the percentage differences we observed were well above this cutoff range. This suggests that our findings are not purely the result of assay variability.

Time to blood draw, naivety to the relevant HPV type, and HIV viral load were important predictors of peak antibody response in univariable, multivariable, and sensitivity analyses. The relationship between age and peak antibody response was less clearly defined, with age not a significant predictor of antibody response to HPV6, 11, but a significant predictor of antibody response to HPV16 and 18. A previous study in women without HIV has noted the same association between increasing age and decreasing peak HPV18 antibody titer [17]. Additionally, this finding is supported by biological understandings of immune system changes with age, resulting in reduced immunogenicity to many vaccines [18]. The relationship between time to blood draw following last vaccine dose and peak antibody titer was expected due to known antibody titer dynamics [19] and therefore needed to be included in the models. Additionally, the relationship between naivety to the relevant HPV type and peak antibody titer was also expected based on prior data demonstrating higher antibody titers post-vaccination among women who are seropositive from natural exposure prior to vaccination [20, 21].

We were limited in our ability to assess the impact of reduced dose schedules in this cohort due to high vaccine schedule adherence leading to small numbers of participants in the one and two-dose groups. Due to the fact that most participants

227 received all doses within seven months, further studies are needed to confirm our finding
228 that the spacing of three dose schedules, up to a range of two years, does not
229 meaningfully impact peak antibody response. Additional studies are also needed to assess
230 the immunogenicity of one and two-dose schedules in WLWH. An additional limitation
231 of this analysis was the use of antibody titers as a surrogate outcome in place of infection
232 and disease endpoints, but low rates of these endpoints precluded their use.
233 These findings are critical to vaccine programming and provision globally. Our
234 analysis suggests that deviations in dose spacing up to two years do not meaningfully
235 impact peak antibody titer; therefore, restarting the vaccine schedule or adding an
236 additional dose in these situations is not needed. As previously described [14], achieving
237 an undetectable HIV viral load should be a key goal not only for HIV disease control and
238 transmission prevention but also to achieve optimal HPV vaccine immune response.
239 Additionally, these findings pertain to WLWH, who accounted for approximately 17.4
240 million of the women aged ≥15 globally in 2014 [22]. Reaching the global target of
241 cervical cancer elimination will require specific intervention targeting this important
242 subset of women who experience a much higher burden of HPV and cervical cancer.
243
244 **Conclusions**
245 Taking into account age, time to serology, CD4 cell count, CD4 nadir, HIV viral
246 load, and HPV naivety, spacing of the three qHPV vaccine doses did not significantly
247 impact peak anti-HPV antibody titers.
248
249 **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); 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), Sandra Blitz, MSc (University Health Network), Jan Christilaw, MD (University of British Columbia), Jeffrey Cohen, MD (Windsor Regional Hospital HIV Care Program), Andrew Coldman, PhD (British Columbia Cancer Agency), François Coutlée, MD (l'Université de Montréal), Simon Dobson, MD (Vaccine Evaluation Centre), Laurie Edmiston (Canadian AIDS Treatment Information Exchange), Catherine Hankins, MD, PhD (Amsterdam Institute for Global Health and Development), Mel Krajden, MD (British Columbia Centre for Disease Control), Marette Lee, MD (University of British Columbia), Jessica McAlpine, MD (University of British Columbia), Dianne Miller, MD (University of British Columbia), Dirk van Niekerk, MD (British Columbia Cancer Agency), Neora Pick, MD (University of British Columbia), 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 contributions to participant enrollment and study visits. We would also like to thank the participants without whom this research would not be possible.

Disclosure of Interests

Ms. McClymont has no conflicts.

Dr. Ogilvie is a co-investigator on an investigator-led trial funded by Hologic Inc and Roche.

Dr. Albert has no conflicts.

Dr. Johnston has no conflicts.

Dr. Raboud is a co-investigator on three projects outside the submitted work, with in-kind contributions or financial support from Merck and Gilead Sciences.

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

Ms. Lipsky has no conflicts.

Dr. Loutfy has received grant and honoraria funding from Merck Canada Inc., ViiV Healthcare, and Gilead, unrelated to the submitted work.

296 Dr. Trottier has received grants from ViiV Healthcare, Gilead, GlaxoSmithKline, and
297 Merck, outside the submitted work.
298 Dr. Smaill received grant and honoraria funding from Merck Canada Inc., ViiV
299 Healthcare, and Gilead, unrelated to the submitted work.
300 Dr. Yudin has no conflicts.
301 Dr. Klein has received funding for investigator-initiated research from ViiV and Merck,
302 unrelated to this work, and honoraria for participation in advisory boards from Merck,
303 ViiV, and BMS.
304 Dr. Harris has received grants, paid to the institution, from the Canadian Institutes of
305 Health Research (CIHR) and honoraria for consultancy and/or speaking engagements
306 from Gilead Sciences Canada Inc., Merck Canada Inc., and ViiV Healthcare, outside the
307 submitted work.
308 Dr. Wobeser has received grants, paid to the institution, from CIHR and Merck Canada
309 Inc., as well as honoraria for consultancy and/or speaking engagements from ViiV
310 Healthcare, Gilead, AbbVie, and Janssen outside of the submitted work.
311 Dr. Bitnun has no conflicts.
312 Dr. Kakkar has no conflicts.
313 Dr. Samson has no conflicts.
314 Dr. Brophy has received honoraria for consultancy work from Merck Canada Inc.,
315 outside the submitted work.
316 Dr. Karatzios has no conflicts.
317 Dr. Money has received grants from GSK and Merck Canada Inc. for conducting
318 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] Arbyn M, Xu L, Simoens C, Martin-Hirsch PP. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. The Cochrane database of systematic reviews. 2018;5:CD009069.

[2] Markowitz LE, Dunne EF, Saraiya M, Lawson HW, Chesson H, Unger ER, et al. Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and Mortality Weekly Report: Recommendations and Reports. 2007;56:1-23.

[3] Dobson SRM, McNeil S, Dionne M, Dawar M, Ogilvie G, Krajden M, et al. Immunogenicity of 2 Doses of HPV Vaccine in Younger Adolescents vs 3 Doses in Young Women: A Randomized Clinical Trial. JAMA. 2013;309:1793-802.

[4] Sankaranarayanan R, Joshi S, Muwonge R, Esmy PO, Basu P, Prabhu P, et al. Can a single dose of human papillomavirus (HPV) vaccine prevent cervical cancer? Early findings from an Indian study. Vaccine. 2018;36:4783-91.

[5] LaMontagne DS, Thiem VD, Huong VM, Tang Y, Neuzil KM. Immunogenicity of Quadrivalent HPV Vaccine Among Girls 11 to 13 Years of Age Vaccinated Using Alternative Dosing Schedules: Results 29 to 32 Months After Third Dose. The Journal of Infectious Diseases. 2013;208:1325-34.

[6] Russell K, Dunne EF, Kemper AR, Dolor RJ, Unger ER, Panicker G, et al. Antibody responses among adolescent females receiving the quadrivalent HPV vaccine series corresponding to standard or non-standard dosing intervals. Vaccine. 2015;33:1953-8.

[7] Gilca V, Sauvageau C, Boulianne N, De Serres G, Crajden M, Ouakki M, et al. The effect of a booster dose of quadrivalent or bivalent HPV vaccine when administered to girls previously vaccinated with two doses of quadrivalent HPV vaccine. Human Vaccines & Immunotherapeutics. 2015;11:732-8.

[8] Lazcano-Ponce E, Torres-Ibarra L, Cruz-Valdez A, Salmerón J, Barrientos-Gutiérrez T, Prado-Galbarro J, et al. Persistence of Immunity When Using Different Human Papillomavirus Vaccination Schedules and Booster-Dose Effects 5 Years After Primary Vaccination. The Journal of infectious diseases. 2019;219:41-9.

[9] WHO. Draft: Global Strategy Towards the Elimination of Cervical Cancer as a Public Health Problem. 2019.

[10] Massad LS, Xie X, Burk R, Keller MJ, Minkoff H, D'Souza G, et al. Long-term cumulative detection of human papillomavirus among HIV seropositive women. AIDS. 2014;28:2601-8.

363 [11] Sun X-W, Kuhn L, Ellerbrock TV, Chiasson MA, Bush TJ, Wright TC. Human
364 Papillomavirus Infection in Women Infected with the Human Immunodeficiency Virus.
365 The New England Journal of Medicine. 1997;337:1343-9.
366 [12] Denslow SA, Rositch AF, Firnhaber C, Ting J, Smith JS. Incidence and progression
367 of cervical lesions in women with HIV: a systematic global review. London, England:
368 SAGE Publications; 2014. p. 163-77.
369 [13] McClymont E, Lee M, Raboud J, Coutlée F, Walmsley S, Lipsky N, et al. The
370 Efficacy of the Quadrivalent Human Papillomavirus Vaccine in Girls and Women Living
371 with HIV. Clinical infectious diseases. 2018.
372 [14] Money DM, Moses E, Blitz S, Vandriel SM, Lipsky N, Walmsley SL, et al. HIV
373 viral suppression results in higher antibody responses in HIV-positive women vaccinated
374 with the quadrivalent human papillomavirus vaccine. Vaccine. 2016;34:4799-806.
375 [15] Lowy DR, Herrero R, Hildesheim A, Participants in the INCIwoPEfPHPVVT.
376 Primary endpoints for future prophylactic human papillomavirus vaccine trials: towards
377 infection and immunobridging. The Lancet Oncology. 2015;16:e226-e33.
378 [16] Dias D, Van Doren J, Schlottmann S, Kelly S, Puchalski D, Ruiz W, et al.
379 Optimization and validation of a multiplexed luminex assay to quantify antibodies to
380 neutralizing epitopes on human papillomaviruses 6, 11, 16, and 18. Clinical and
381 diagnostic laboratory immunology. 2005;12:959-69.
382 [17] Castellsagué X, Muñoz N, Pitisuttithum P, Ferris D, Monsonego J, Ault K, et al.
383 End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16,
384 18) recombinant vaccine in adult women 24-45 years of age. British Journal of Cancer.
385 2011;105:28-37.

386 [18] Lord JM. The effect of ageing of the immune system on vaccination responses.
387 Human vaccines & immunotherapeutics. 2013;9:1364-7.
388 [19] Joura EA, Kjaer SK, Wheeler CM, Sigurdsson K, Iversen O-E, Hernandez-Avila M,
389 et al. HPV antibody levels and clinical efficacy following administration of a
390 prophylactic quadrivalent HPV vaccine. Vaccine. 2008;26:6844-51.
391 [20] Poland GA, Jacobson RM, Koutsky LA, Tamms GM, Railkar R, Smith JF, et al.
392 Immunogenicity and reactogenicity of a novel vaccine for human papillomavirus 16: a 2-
393 year randomized controlled clinical trial. Mayo Clinic proceedings. 2005;80:601.
394 [21] Villa LL, Ault KA, Giuliano AR, Costa RLR, Petta CA, Andrade RP, et al.
395 Immunologic responses following administration of a vaccine targeting human
396 papillomavirus Types 6, 11, 16, and 18. Vaccine. 2006;24:5571-83.
397 [22] WHO. Global Health Observatory Data. 2019.
398
399

400 Table 1. Participant characteristics by vaccine spacing category
401

Characteristic	**Within 7 months** (n=229)	**7 months-1 year** (n=56)	**1 to 2 years** (n=22)	**Chi squared test for trend or Spearman's rank coefficient test** (p value)	**All participants** (n=307)
Baseline age (years)+	37 (23-44)	35 (30-38)	36 (30-40)	0.47	36 (26-44)
Baseline CD4 count (cells/mm^3)					
<200	7 (3%)	4 (7%)	2 (9%)	0.02	13 (4%)
200-500	86 (38%)	24 (43%)	12 (55%)		122 (40%)
>500	122 (53%)	25 (45%)	8 (36%)		155 (50%)
Baseline CD4 nadir (cells/mm^3)+	240 (122-370)	255 (160-356)	200 (80-320)	0.64	240 (122-365)
Baseline HIV viral load undetectable (<50 copies/mL)					
Yes	158 (69%)	33 (59%)	13 (59%)	0.09	204 (66%)
No	58 (25%)	18 (32%)	9 (41%)		85 (28%)
Unknown	13 (6%)	5 (9%)	0		18 (6%)
Naïve to HPV6	149 (65%)	27 (49%)	14 (64%)	0.71	102 (33%)
Naïve to HPV11	195 (85%)	39 (70%)	13 (59%)	<0.01	206 (67%)
Naïve to HPV16	155 (68%)	35 (63%)	11 (50%)	0.09	201 (65%)
Naïve to HPV18	197 (86%)	40 (71%)	19 (86%)	0.43	215 (70%)
Time to blood draw post-last dose (days)+	31 (28-39)	43 (30-100)	80.5 (41-177)	<0.001	34 (28-46)
Peak HPV6 log titer+	6.4 (5.5-7.1)	6.7 (5.6-7.3)	6.1 (5.2-7.1)	0.57	6.4 (5.5-7.2)
Peak HPV11 log titer+	6.4 (5.8-7.1)	6.5 (5.8-7.1)	6.3 (5.5-6.6)	0.57	6.4 (5.8-7.1)
Peak HPV16 log titer+	7.8 (7.1-8.4)	7.6 (6.7-8.4)	7.2 (5.6-8.0)	0.05	7.7 (6.9-8.4)
Peak HPV18 log titer+	5.9 (4.8-6.8)	5.8 (4.8-6.7)	5.1 (4.2-5.8)	0.14	5.8(4.8-6.7)

402
403 + median, interquartile range
404
405
406
407
408
409
410
411
412 Table 2. Univariable and multivariable linear regression results for each HPV type
413 assessing the impact of each variable on peak HPV log titer.

414

	Univariable linear regression				Multivariable linear regression			
HPV6								
Variable	**P value**	**β[a]**	**Exp β[b]**	**95% CI[c]**	**P value**	**β**	**Exp β**	**95% CI**
Baseline age (years, in increments of 10)	0.07	-0.10	0.91	0.82-1.01	0.11	-0.12	0.88	0.75-1.03
Baseline CD4 count (cells/mm^3)								
<200	0.29	Ref	Ref	-	0.77	Ref	Ref	-
200-500		0.34	1.41	0.70-2.85		0.25	1.29	0.63-2.61
>500		0.49	1.63	0.81-3.28		0.23	1.26	0.61-2.61
Baseline CD4 nadir (cells/mm^3, in increments of 100)	0.58	0.02	1.02	0.95-1.09	0.87	-0.008	0.99	0.90-1.09
Baseline HIV viral load undetectable (<50 copies/mL)								
Yes	<0.001	Ref	Ref	-	0.005	Ref	Ref	-
No		-0.52	0.59	0.44-0.80		0.49	0.61	0.43-0.87
Naïve to HPV6								
Yes	0.001	Ref	Ref	-	<0.001	Ref	Ref	-
No		0.48	1.61	1.20-2.16		0.57	1.77	1.32-2.38
Time to blood draw post-last dose (days)	<0.001	-0.004	0.99	0.99-1.00	<0.001	-0.004	0.99	0.99-1.00
Dose spacing category								
Within 7 months	0.40	Ref	Ref	-	0.17	Ref	Ref	-
7 months-1 year		0.16	1.17	0.82-1.67		0.35	1.42	0.97-2.09
1-2 years		-0.25	0.78	0.46-1.33		0.22	1.25	0.71-2.18
HPV11								
Variable	**P value**	**β**	**Exp β**	**95% CI**	**P value**	**β**	**Exp β**	**95% CI**
Age (years, in increments of 10)	0.36	-0.05	0.95	0.86-1.06	0.56	-0.04	0.96	0.83-1.11
CD4 count (cells/mm^3)								
<200	0.17	Ref	Ref	-	0.71	Ref	Ref	-
200-500		0.42	1.52	0.77-3.02		0.20	1.22	0.63-2.35
>500		0.58	1.79	0.91-3.52		0.10	1.10	0.56-2.18
CD4 nadir (cells/mm^3, in increments of 100)	1.00	9.9e-6	1.00	0.94-1.07	0.86	0.007	1.01	0.92-1.10
HIV viral load undetectable (<50 copies/mL)								
Yes	<0.001	Ref	Ref	-	<0.001	Ref	Ref	-
No		-0.75	0.47	0.35-0.62		0.81	0.44	0.32-0.61
Naïve to HPV11								
Yes	0.007	Ref	Ref	-	<0.001	Ref	Ref	-
No		0.47	1.60	1.14-2.25		0.56	1.74	1.25-2.43
Time to blood draw post-last dose (days)	<0.001	-0.005	0.99	0.99-1.00	<0.001	-0.004	0.99	0.99-1.00
Dose spacing category								
Within 7 months	0.52	Ref	Ref	-	0.81	Ref	Ref	-
7 months-1 year		-0.05	0.95	0.67-1.35		0.08	1.08	0.75-1.55

1-2 years		-0.30	0.74	0.44-1.25		0.15	1.16	0.69-1.97
HPV16								
Variable	**P value**	**β**	**Exp β**	**95% CI**	**P value**	**β**	**Exp β**	**95% CI**
Age (years, in increments of 10)	0.009	-0.16	0.86	0.76-0.96	<0.001	-0.24	0.78	0.69-0.88
CD4 count (cells/mm^3)								
<200	0.05	Ref	Ref	-	0.69	Ref	Ref	-
200-500		0.14	1.15	0.53-2.50		-0.1	0.91	0.45-1.85
>500		0.51	1.67	0.77-3.60		0.04	1.04	0.50-2.15
CD4 nadir (cells/mm^3, in increments of 100)	0.56	0.02	1.02	0.95-1.10	0.23	-0.05	0.95	0.88-1.03
HIV viral load undetectable (<50 copies/mL)								
Yes	<0.001	Ref	Ref	-	<0.001	Ref	Ref	-
No		-0.72	0.49	0.35-0.67		-0.66	0.52	0.37-0.71
Naïve to HPV16								
Yes	0.17	Ref	Ref	-	0.02	Ref	Ref	-
No		0.22	1.25	0.91-1.72		0.36	1.44	1.07-1.94
Time to blood draw post-last dose (days)	<0.001	-0.007	0.99	0.99-0.99	<0.001	-0.01	0.99	0.99-0.99
Dose spacing category								
Within 7 months	0.08	Ref	Ref	-	0.95	Ref	Ref	-
7 months-1 year		-0.23	0.80	0.54-1.18		0.05	1.06	0.73-1.53
1-2 years		-0.62	0.54	0.30-0.98		0.06	1.06	0.60-1.87
HPV18								
Variable	**P value**	**β**	**Exp β**	**95% CI**	**P value**	**β**	**Exp β**	**95% CI**
Age (years, in increments of 10)	0.07	-0.12	0.89	0.78-1.01	0.02	-0.21	0.81	0.68-0.97
CD4 count (cells/mm^3)								
<200	0.03	Ref	Ref	-	0.92	Ref	Ref	-
200-500		0.17	1.18	0.50-2.80		-0.002	1.00	0.46-2.17
>500		0.61	1.84	0.79-4.32		0.07	1.07	0.48-2.39
CD4 nadir (cells/mm^3, in increments of 100)	0.99	$6.9x10^{-4}$	1.00	0.92-1.08	0.75	-0.02	0.98	0.89-1.09
HIV viral load undetectable (<50 copies/mL)								
Yes	<0.001	Ref	Ref	-	<0.001	Ref	Ref	-
No		-1.02	0.36	0.25-0.52		1.03	0.36	0.25-0.52
Naïve to HPV18								
Yes	0.003	Ref	Ref	-	0.007	Ref	Ref	-
No		0.68	1.98	1.27-3.09		0.55	1.74	1.15-2.63
Time to blood draw post-last dose (days)	<0.001	-0.007	0.99	0.99-0.99	<0.001	-0.006	0.99	0.99-1.00
Dose spacing category								
Within 7 months	0.02	Ref	Ref	-	0.51	Ref	Ref	-
7 months-1 year		0.02	1.02	0.66-1.59		0.15	1.16	0.76-1.77
1-2 years		-0.91	0.40	0.21-0.77		-0.24	0.79	0.43-1.46

[a] Coefficients from the linear regressions in natural log units of peak HPV antibody titer.
[b] Exponentiated coefficients ($e^{coefficient}$) from the linear regression models. This gives the results in terms of a ratio of geometric mean peak antibody titers on the original scale [log(A) – log(B) = log(A/B)], and can be interpreted as percent difference (e.g. 0.80 would indicate that the peak antibody titers were 20% lower on average in the category of interest compared to the reference category, while a value of 2 would indicate that the peak antibody titer was 200% (2 times) higher in the category of interest compared to the reference category. A value of 1 indicates no difference between the groups in antibody titers).
[c] 95% CI of the exponentiated coefficients.