HPV vaccination and HIV preexposure prophylaxis (PrEP): Missed opportunities for anal cancer prevention among at risk populations

Christopher W. Wheldon

Department of Social and Behavioral Sciences, College of Public Health, Temple University, Philadelphia, PA, USA

ABSTRACT
Gay, bisexual, and other men who have sex with men (GBM), in addition to transgender women who have sex with men (TW) are at disproportionate risk for anal cancer. The necessary and sufficient cause of anal cancer is oncogenic HPV infection. However, co-existing sexually transmitted infections (STIs), including human immunodeficiency virus (HIV), syphilis, and gonorrhea may amplify the risk of anal cancer in the presence of oncogenic HPV. The synergistic relationship between HPV, concurrent STIs, and related behavioral factors (e.g., unprotected receptive anal intercourse [URAI]) is thought to contribute to a syndemic of anal cancer risk disproportionally impacting GBM and TW.

The 9-valent HPV vaccine is proven safe and effective at preventing oncogenic HPV infection in GBM up through age 26 and has shown to be highly immunogenic among mid-adult men aged 27 to 45. The 9-valent vaccine is currently licensed for adults up through age 45. Catchup vaccination is recommended for all adults up through age 26 and shared clinical decision-making (SCDM) for adults 27 to 45. As of 2017, just 32.8% of GBM 18–26 had received at least 1 dose of HPV vaccine. Coverage is even lower among mid-adult GBM: 22.2% for those aged 27 to 30 and 13.5% for those aged 31 to 40. There is limited evidence for vaccine uptake among TW.

Acceptability is high for HPV vaccination among GBM and TW. Low uptake of HPV vaccination is likely a result of low awareness and missed opportunities during primary care. Qualitative research has identified the need for alternative strategies for HPV vaccine delivery to increase convenience and availability for GBM and TW populations. Promoting HPV vaccination during the clinical management of pre-exposure prophylaxis (PrEP) is an unexplored strategy.
The brief questionnaire (15 minutes to complete) was available in either English or Spanish. A single item was used to identify PrEP users for this analysis: “Are you currently taking PrEP (Pre-Exposure Prophylaxis)?” Responses were recorded as either yes or no. Additional measures used in this analysis are described below.

**HPV vaccination**

A single item measured HPV vaccine uptake: “Have you received the HPV vaccine (sometimes called Gardasil or Cervarix)?” Responses were recorded as either yes, no, or I don’t know. Those who responded yes to this item were coded as having initiated HPV vaccination. Recall of HPV vaccination was high in a sensitivity analysis of adult GBM. 18

**Sexual orientation and gender identity (SOGI)**

Sexual orientation was operationalized as sexual identity. Due to low cell sizes gay/lesbian, bisexual/pansexual, and all other identities were collapsed into three categories. A two-step approach was used to assess gender identity. 19 Sex at birth and current gender identity were used to code participants as cisgender men (i.e., male sex at birth and current man) or transgender women (male sex at birth and current woman).

**Healthcare utilization**

Participants who responded yes to “Do you have one person you think of as your personal doctor or health care provider?” were coded as having a medical home. Additionally, receipt of the following three health services were assessed: Past year influenza vaccination (“flu shot” or “flu vaccine sprayed in nose”), hepatitis A vaccination, and past year treatment for a “sexually transmitted disease or infection” (STI).

**Anal cancer risk factors**

Two anal cancer risk factors were assessed: current cigarette smoking (i.e., currently smoked cigarettes some days or every day) and any past year occurrence of unprotected receptive anal sex (i.e., “receptive anal sex [bottoming] without a condom”).

**Sociodemographic factors**

Demographic factors included age, race, ethnicity, and educational attainment. Age was categorized to include participants in the catchup vaccine range (i.e., 18–26), those who were in the catchup age at some point since the vaccine was indicated for anal cancer in 2011 (i.e., those currently 27 to 35), and those who were never in the catchup age (i.e., 36–45). The 27 to 45 age cohorts represent adults who fall under the SCDM recommendation. Participants reported their county of residence, which was used to classify them as rural or urban based on The Center for Rural Pennsylvania’s definition of population density. 20 Financial insecurity was defined as participants with “just enough money to make ends meet or not enough money to make ends meet” at the end of a month.

The sample for this study included GBM or TW between 18 and 45 years of age who were currently taking PrEP for HIV prevention (N = 284). This study focused on GBM and TW because these populations are at greatest risk for anal cancer and make up the highest percentage of PrEP patients. 21,22 Out of this subsample, 10 cases had missing data on the independent variables. Thus, the analytic sample for the complete case analyses reported here was 274. Bivariate differences were examined using Chi-square test of independence. HPV vaccine initiation was regressed on the predictor variables using bivariate logistic regression (SAS Institute, Cary, NC). Crude and age-adjusted prevalence ratios were reported as the measures of association.

Sample characteristics are reported in Table 1. Overall, 43.8% of the sample had initiated HPV vaccination. Initiation of HPV vaccination was highest among those aged 18 to 26 and decreased among the older age cohorts (Figure 1). Among PrEP users, 32.2% (aged 18–26), 56.5% (aged 27–35), and 74.0% (aged 36–45) had not initiated HPV vaccination.

The prevalence of HPV vaccine initiation was significantly lower among respondents 27 to 35 (PR = 0.64; 95% CI: 0.49–0.83) and 36 to 45 (PR = 0.38; 95% CI: 0.25–0.58). Respondents who had received Hepatitis A vaccination were significantly more likely to have had initiated HPV vaccination after adjusting for age (aPR = 2.60; 95% CI: 1.75–3.84). No other factors were associated with HPV vaccine initiation.

More than half of GBM and TW engaged in PrEP care had not previously initiated HPV vaccination and represent potential missed opportunities for anal cancer prevention. Nearly a third of participants in the catchup age range and 60% in the mid-adult group were not vaccinated. It is unknown how many of these PrEP users were recommended to get vaccinated or engaged in SCDM. Previous research suggests that providers are not routinely engaging GBM in discussion about HPV vaccination and GBM have limited awareness of anal cancer. 10, 23 Future research should determine to what extent PrEP providers are discussing HPV, anal cancer, and/or HPV vaccinations with their PrEP patients.

HPV vaccination was not associated with known anal cancer risk factors suggesting that targeted promotion may not be routinely occurring. Nor was HPV vaccination associated with health-care utilization apart from Hepatitis A vaccination. Screening for Hepatitis A immunity is not currently apart from routine PrEP care 24; however, the strong correlation between Hepatitis A and HPV vaccination suggest that some PrEP patients are advocating for themselves or some PrEP providers are ensuring that their patients have received available vaccinations against STIs. These efforts should be expanded to include HPV vaccination.

The non-probability sample within one US state and the community-based recruitment strategies make it impossible to calculate a response rate and limit the generalizability of the findings. The small sample size may also have limited power to detect differences across predictor variables with limited distributions. In addition, the measures used self-report for vaccination status and did not allow for the differentiation of HPV vaccine initiation and completion. Further details regarding PrEP use, such as length of time on PrEP and adherence, were also not available in the dataset.
Table 1. Sample characteristics and correlates of HPV vaccine initiation among GBM and transgender women who are currently using pre-exposure prophylaxis for HIV prevention (PrEP), N = 274.

| Characteristic                          | Total | HPV Vaccine Initiation |
|----------------------------------------|-------|------------------------|
|                                        | N (%) | Yes n (%) | No n (%) | Crude Prevalence Ratio (95% CI) | Age-adjusted Prevalence Ratio (95% CI) |
| **Total**                              |       |            |          |                               |                                       |
| **Demographics**                       |       |            |          |                               |                                       |
| Age                                    |       |            |          |                               |                                       |
| 18–26 (ref)                            | 59 (21.5) | 40 (67.8) | 19 (32.2) | 1.0                           |                                         |
| 27 – 35                                | 138 (50.4) | 60 (43.5) | 78 (56.5) | **0.64 (0.49–0.83)**          | **1.06 (0.51–1.84)**                    |
| 36 – 45                                | 77 (28.1) | 20 (26.0) | 57 (74.0) | **0.38 (0.25–0.58)**          | **1.06 (0.51–1.84)**                    |
| Hispanic/Latinx                        |       |            |          |                               |                                       |
| No (ref)                               | 252 (92.0) | 114 (45.2) | 138 (54.8) | 1.0                           | 1.0                                     |
| Yes                                    | 22 (8.0) | 6 (27.3)   | 16 (72.7) | 0.60 (0.30–1.21)              | 0.61 (0.31–1.20)                        |
| Race                                   |       |            |          |                               |                                       |
| White (ref)                            | 232 (84.7) | 104 (44.8) | 128 (55.2) | 1.0                           | 1.0                                     |
| Black/African American                 | 14 (5.1) | 4 (28.6)   | 10 (71.4) | 1.57 (0.68–3.64)              | 1.63 (0.73–3.68)                        |
| Another race                           | 28 (10.2) | 12 (42.9)  | 16 (57.1) | 1.05 (0.67–1.64)              | 1.14 (0.75–1.73)                        |
| College degree                         |       |            |          |                               |                                       |
| No (ref)                               | 90 (32.9) | 38 (42.2)  | 52 (57.8) | 1.0                           | 1.0                                     |
| Yes                                    | 184 (67.1) | 82 (44.6)  | 102 (55.4) | 1.06 (0.79–1.41)              | 1.30 (0.99–1.70)                        |
| Financial security                     |       |            |          |                               |                                       |
| No (ref)                               | 105 (38.3) | 44 (41.9)  | 61 (58.1) | 1.0                           | 1.0                                     |
| Yes                                    | 169 (61.7) | 76 (45.0)  | 93 (55.0) | 1.07 (0.81–1.42)              | 1.11 (0.86–1.43)                        |
| Rural county residence                 |       |            |          |                               |                                       |
| No (ref)                               | 244 (89.0) | 103 (42.2) | 141 (57.8) | 1.0                           | 1.0                                     |
| Yes                                    | 30 (11.0) | 17 (56.7)  | 13 (43.3) | 1.34 (0.95–1.90)              | 1.23 (0.91–1.66)                        |
| **SOGI**                               |       |            |          |                               |                                       |
| Sexual orientation                     |       |            |          |                               |                                       |
| Gay/Lesbian (ref)                      | 242 (88.3) | 109 (45.0) | 133 (55.0) | 1.0                           | 1.0                                     |
| Bisexual/Pansexual                     | 25 (9.1) | 8 (32.0)   | 17 (68.0) | 1.41 (0.78–2.33)              | 1.22 (0.69–2.15)                        |
| Other                                  | 7 (2.6) | 3 (42.9)   | 4 (57.1)  | 1.05 (0.44–2.50)              | 0.86 (0.37–2.00)                        |
| Gender identity                        |       |            |          |                               |                                       |
| Cisgender Man (ref)                    | 265 (96.7) | 119 (44.9) | 146 (55.1) | 1.0                           | 1.0                                     |
| Transgender Woman                      | 9 (3.3) | 1 (11.1)   | 8 (88.9)  | 0.25 (0.04–1.58)              | 0.26 (0.04–1.61)                        |
| **Healthcare utilization**             |       |            |          |                               |                                       |
| Medical home                           |       |            |          |                               |                                       |
| No (ref)                               | 31 (11.3) | 14 (45.2)  | 17 (54.8) | 1.0                           | 1.0                                     |
| Yes                                    | 243 (88.7) | 106 (43.6) | 137 (56.4) | 0.97 (0.64–1.46)              | 0.99 (0.68–1.44)                        |
| Flu                                    |       |            |          |                               |                                       |
| No (ref)                               | 102 (37.2) | 40 (39.2)  | 62 (60.8) | 1.0                           | 1.0                                     |
| Yes                                    | 172 (62.8) | 80 (46.5)  | 92 (53.5) | 1.19 (0.89–1.59)              | 1.26 (0.97–1.64)                        |
| Hep A                                  |       |            |          |                               |                                       |
| No (ref)                               | 91 (33.2) | 20 (22.0)  | 71 (78.0) | 1.0                           | 1.0                                     |
| Yes                                    | 183 (66.8) | 100 (54.6) | 83 (45.4) | **2.49 (1.65–3.74)**         | **2.60 (1.75–3.84)**                    |
| STI Treatment                          |       |            |          |                               |                                       |
| No (ref)                               | 148 (54.0) | 58 (39.2)  | 90 (60.8) | 1.0                           | 1.0                                     |
| Yes                                    | 126 (46.0) | 62 (49.2)  | 64 (50.8) | 1.26 (0.96–1.64)              | 1.20 (0.94–1.53)                        |
| **Anal Cancer Risk Factors**           |       |            |          |                               |                                       |
| Tobacco cigarette user                 |       |            |          |                               |                                       |
| No (ref)                               | 234 (85.4) | 104 (44.4) | 130 (55.6) | 1.0                           | 1.0                                     |
| Yes                                    | 40 (14.6) | 16 (40.0)  | 24 (60.0) | 0.90 (0.60–1.35)              | 0.93 (0.63–1.36)                        |
| Unprotected receptive anal intercourse, past year |       |            |          |                               |                                       |
| No (ref)                               | 82 (29.9) | 29 (35.4)  | 53 (64.6) | 1.0                           | 1.0                                     |
| Yes                                    | 192 (70.1) | 91 (47.4)  | 101 (52.6) | 1.34 (0.97–1.86)              | 1.24 (0.91–1.69)                        |

Bolded prevalence ratios are statistically significant at p < .05.
Provider recommendation is a major determinant of HPV vaccination among GBM and HPV vaccine acceptability is high among GBM and TW. Major barriers are availability and convenience. PrEP management visits are a potential venue for targeted HPV vaccine promotion. Ensuring that all PrEP patients 18 to 26 are fully vaccinated against HPV and those 27 to 45 are engaged in SCDM will help to extend the reach of anal cancer prevention. Incorporating HPV vaccination into national PrEP guidelines would help promote equitable patient-centered care.

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ORCID
Christopher W. Wheldon http://orcid.org/0000-0002-0452-0252

References
1. Grulich AE, Poynten IM, Machalek DA, Jin F, Templeton DJ, Hillman RJ. The epidemiology of anal cancer. Sex Health. 2012;9:504. doi:10.1071/SH12070.
2. McCloskey JC, Martin Kast W, Flexman JP, McCallum D, French MA, Phillips M. Syndemic synergy of HPV and other sexually transmitted pathogens in the development of high-grade anal squamous intraepithelial lesions. Papillomavirus Res. 2017;4:90–98. doi:10.1016/j.pvr.2017.10.004.
3. Palefsky JM, Giuliano AR, Goldstone S, Moreira ED, Aranda C, Jessen H, Hillman R, Ferris D, Coutlee F, Stoler MH, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N Engl J Med. 2011;365:1576–1585. doi:10.1056/NEJMoa1010971.
4. Giuliano AR, Isaacs-Soriano K, Torres BN, Abrahamsen M, Ingles DJ, Sirak BA, Quiterio M, Lazcano-Ponce E. Immunogenicity and safety of Gardasil among mid-adult aged men (27–45 years)—the MAM study. Vaccine. 2015;33:5640–5646. doi:10.1016/j.vaccine.2015.08.072.
5. Meites E, Sziilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human papillomavirus vaccination for adults: updated recommendations of the advisory committee on immunization practices. Morb Mortal Wkly Rep. 2019;68:698–702. doi:10.15585/mmwr.mm6832a3.
6. McClung N, Burnett J, Wejnert C, Markowitz LE, Meites E. Human papillomavirus vaccination coverage among men who have sex with men—National HIV Behavioral Surveillance, United States, 2017. Vaccine. 2020;38:7417–7421.
7. Pho AT, Mangal S, Bakken S. Human papillomavirus vaccination among transgender and gender diverse people in the United States: an integrative review. Transgender Health. 2021. ahead of print. doi:10.1089/trgh.2020.0174.
8. Nadarzynski T, Frost M, Miller D, Wheldon CW, Wiernik BM, Zou H, Richardson D, Marlow LAV, Smith H, Jones CJ, et al. Vaccine acceptability, uptake and completion amongst men who have sex with men: a systematic review, meta-analysis and theoretical framework. Vaccine. 2021;39:3565–3581. doi:10.1016/j.vaccine.2021.05.013.
9. Meites E, Krishna NK, Markowitz LE, Oster AM. Health care use and opportunities for human papillomavirus vaccination among young men who have sex with men. Sex Transm Dis. 2013;40:154–157. doi:10.1097/OLQ.0b013e31827b9e89.
10. Wheldon CW, Sutton SK, Fontenot HB, Quinn GP, Giuliano AR, Vadaparampil ST. Physician communication practices as a barrier to risk-based HPV vaccine uptake among men who have sex with men. J Cancer Educ. 2018;33:1126–1131. doi:10.1007/s13187-017-1223-6.
11. Wheldon CW, Buhi ER, Daley EM. Gay and bisexual men’s human papillomavirus vaccineentions: a theory-based structural equation analysis. J Health Psychol. 2013;18:1177–1186. doi:10.1177/1359105312459875.
12. Wheldon CW, Daley EM, Buhi ER, Baldwin JA, Nyitraay AG, Giuliano AR. HPV vaccine decision-making among young men who have sex with men. Health Educ J. 2017;76:52–63. doi:10.1177/0017869616647989.
13. Nadarzynski T, Smith H, Richardson D, Pollard A, Llewellyn C. Perceptions of HPV and attitudes towards HPV vaccination amongst men who have sex with men: a qualitative analysis. Br J Health Psychol. 2017;22:345–361. doi:10.1111/bjhp.12233.
14. National Clinician Consultation Center. PrEP guidelines & resources [Internet]; [accessed 2021 Jul 14]. https://ncce.ucsf.edu/clinical-resources/prep-guidelines-and-resources/.

Figure 1. Initiation of HPV vaccination overall and by age among gay and bisexual men and transgender women who current PrEP users (N = 274).
15. Montaño MA, Dombrowski JC, Dasgupta S, Golden MR, Duerr A, Manhart LE, Barbee LA, Khosropour CM. Changes in sexual behavior and STI diagnoses among MSM initiating PrEP in a clinic setting. AIDS Behav. 2018;23:548–555. doi:10.1007/s10461-018-2252-9.

16. Grov C, Westmoreland DA, D’Angelo AB, Pantalone DW. How has HIV pre-exposure prophylaxis (PrEP) changed sex? A review of research in a new era of bio-behavioral HIV prevention. J Sex Res. 2021;58:891–913.

17. Research & Evaluation Group at Public Health Management Corporation and Bradbury-Sullivan LGBT Community Center. 2020. Pennsylvania LGBTQ Health Needs Assessment.

18. Forward T, Meites E, Lin J, Hughes JP, Unger ER, Markowitz LE, Golden M, Swanson F, Faestel PM, Winer RL. 2021. Sensitivity of self-reported HPV vaccination history among 18–26 year-old men who have sex with men — Seattle, Washington, 2016–2018. Sex Transm Dis. Publish Ahead of Print.

19. Patterson JG, Jabson JM, Bowen DJ. Measuring sexual and gender minority populations in health surveillance. LGBT Health. 2017;4:82–105. doi:10.1089/lgbt.2016.0026.

20. The center for rural Pennsylvania [Internet]. [accessed 2021 Jul 9]. https://www.rural.palegislature.us/rural_urban.html.

21. Clifford GM, Smith JS, Plummer M, Munoz N, Franceschi S. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. Br J Cancer. 2003;88:63–73. doi:10.1038/sj.bjc.6600688.

22. Caponi M, Burgess C, Leatherwood A, Molano LF. Demographic characteristics associated with the use of HIV pre-exposure prophylaxis (PrEP) in an urban, community health center. Prev Med Rep. 2019;15:100889. doi:10.1016/j.pmedr.2019.100889.

23. Wheldon CW, Maness SB, Islam JY, Deshmukh AA, Nyitray AG. Gay and bisexual men in the US lack basic information about anal cancer. J Low Genit Tract Dis. 2021;25:48–52. doi:10.1097/LGT.0000000000000571.

24. Cohall A, Zucker J, Krieger R, Scott C, Guido C, Hakala S, Carnevale C. Missed opportunities for hepatitis a vaccination among MSM initiating PrEP. J Community Health. 2020;45:506–509. doi:10.1007/s10900-019-00768-w.