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# Interest in Hypothetical Preexposure Prophylaxis Against Herpes Simplex Virus: A Cross-Sectional Survey

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**Abstract:** We surveyed 383 men who have sex with men attending sexual health clinics regarding interest in hypothetical preexposure prophylaxis against herpes simplex virus. Overall interest was 62.5% and was associated with the number of different sexually transmitted infections previously diagnosed (adjusted odds ratio, 1.9; 95% confidence interval, 1.5–2.6) and previous HIV preexposure prophylaxis use (adjusted odds ratio, 2.9; 95% confidence interval, 1.1–8.3).

Herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) are common causes of genital ulcer disease.<sup>1,2</sup> Both cause lifelong infections associated with considerable morbidity, stigma,<sup>3</sup> and health care expenditure.<sup>4</sup> HSV-2 is of particular public health concern because it increases the risk of HIV acquisition 2- to 3-fold.<sup>5,6</sup>

Preventing new HSV infections is thus an important objective. Although several vaccine candidates are in development,

obstacles remain.<sup>7</sup> Preexposure prophylaxis (PrEP) is a successful strategy for preventing new HIV infections and may warrant study in clinical trials for HSV prevention if acceptable to populations at risk. Given the high prevalence<sup>8</sup> and incidence<sup>9</sup> of HSV-1 and HSV-2 among gay, bisexual, and other men who have sex with men (gbMSM), this population may be particularly motivated to take HSV PrEP, were it to become available. We quantified interest in hypothetical HSV PrEP among gbMSM attending sexual health clinics in 2 Canadian cities.

## MATERIALS AND METHODS

We approached gbMSM during routine visits to sexual health clinics in Toronto (1 site) and Vancouver (2 sites) and invited them to participate in an anonymous, self-administered questionnaire from June to August 2018. Self-identified gbMSM of any age with adequate English proficiency were eligible. Potential participants read a short letter of information and were deemed to have provided implied consent to participate if they then completed the questionnaire. They received a \$10 CAD gift card upon completion. The questionnaire was administered via paper or electronic tablet; study staff were present to answer questions. All procedures were approved by the Research Ethics Boards of St Michael's Hospital (REB 18-108) and the University of British Columbia (H18-01579).

The primary purpose of the survey was to examine interest in syphilis chemoprophylaxis strategies; those results are published.<sup>10</sup> To examine interest in HSV PrEP, we assumed that this would take the form of a safe, existing, oral antiviral such as valacyclovir, and that delivery models would be similar to HIV PrEP.<sup>11</sup> Participants were presented with an introductory paragraph about HSV (Supplemental Digital Content 1, <http://links.lww.com/OLQ/A593>) and the following description: "Herpes PrEP would involve taking one anti-herpes pill every day to prevent HSV. It probably would NOT cause side effects or drug resistance. It would involve doing blood work and seeing a doctor every three months. If this strategy were approved in Canada and available to you, would you take it?" Response choices were "probably yes," "definitely yes," "probably not," and "definitely not"; we defined the outcome "interested in HSV PrEP" as those responding "probably yes" or "definitely yes" to this question. We did not differentiate between HSV-1 and HSV-2 because we expected that participants would not be familiar with this distinction and because we would not expect major differences in how PrEP for these viruses would work.

Additional items included demographics, HIV and sexually transmitted infection (STI) history, sexual behavior, and knowledge/use of other HIV/STI prevention strategies. We further included brief psychometric tools to screen for depression (Patient Health Questionnaire-2 score  $\geq 2$ ),<sup>12</sup> problem alcohol use (Alcohol Use Disorders Identification Test-C score  $\geq 4$ ),<sup>13</sup> and problem substance use (Drug Use Disorders Identification Test score  $\geq 25$ ).<sup>14</sup>

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After excluding those reporting prior genital/anal herpes, we used descriptive statistics to summarize participant characteristics. To explore differences between the Toronto and Vancouver samples, we conducted *t* tests and  $\chi^2$  tests for continuous and categorical variables, respectively. Next, we calculated the proportion of respondents indicating interest in HSV PrEP as defined previously. In exploratory analyses, we constructed univariable and multivariable logistic regression models quantifying the relationship between respondent characteristics and interest in HSV PrEP. The multivariable model was built using backward selection, starting with all variables and removing the predictor with the largest *P* value iteratively until achieving the model with the lowest Akaike information criterion. We did not use ordinal logistic regression because it generated similar estimates but poorer model fit. Missing data were excluded.

The sample size was predetermined by the primary study on syphilis chemoprophylaxis, which recruited 424 gbMSM.<sup>10</sup> All analyses were done using R, version 3.6.2.

**RESULTS**

Of 424 respondents, 41 were excluded because of prior HSV, leaving 383 eligible participants (58% Toronto, 42% Vancouver; Supplemental Digital Content 2, <http://links.lww.com/OLQ/A594>). Median age was 30 (interquartile range, 25.0–38.7) years,

86.6% self-identified as gay, and 1 participant was transgender male. Most participants were White (53.7%), followed by Asian (28.5%); 5.6% were Black. Most (61.3%) had a college/undergraduate degree or higher, and 58.0% had been diagnosed with at least one STI (gonorrhea, chlamydia, syphilis, genital/anal warts, HIV).

Participants reported a mean of 6.0 (interquartile range, 3.0–12.0) male sex partners in the preceding 6 months. Awareness of HIV PrEP, HIV postexposure prophylaxis (PEP), and human papillomavirus (HPV) vaccination was high, at 70.8%, 54.0%, and 64.4% respectively. Prior use of these technologies was somewhat lower, at 13.1%, 10.3%, and 35.5% respectively.

Overall, 105 (27.7%), 132 (34.8%), 100 (26.4%), and 42 (11.1%) of participants indicated being “definitely,” “probably,” “probably not,” and “definitely not” interested in HSV PrEP, and 4 had missing responses; 237 (61.8%) of 383 thus met our definition of being interested in using it. Univariable logistic regression found that this interest was associated with the number of sexual partners (odds ratio [OR], 1.03 per partner; 95% confidence interval [CI], 1.01–1.06), recruitment in Toronto rather than Vancouver (OR, 2.1; 95% CI, 1.37–3.21), the number of different previously diagnosed STIs (OR, 2.1 per STI; 95% CI, 1.7–2.7), HIV positivity (OR, 6.4; 95% CI, 1.8–40.8), screening positive for depression (OR, 3.13; 95% CI, 1.35–8.55), and disagreeing with the statement, “the only truly effective means of STI prevention is condom use” (OR, 1.72; 95% CI, 1.12–2.69). Willingness was also

**TABLE 1.** Variables Associated With Willingness to Use HSV PrEP

Characteristic	Willing to Use HSV PrEP, n (%)	OR (95% CI)	<i>P</i>	aOR (95% CI)	<i>P</i>
No. male sex partners, past 6 mo (per 1-unit increase)	—	1.03 (1.01–1.06)	0.01		
Location					
Toronto	153 (69.9)	2.1 (1.37–3.21)			
Vancouver	84 (52.5)	1.0	<0.001		
Age	—	0.99 (0.96–1.0)	0.13		
Education					
High school diploma or less	85 (59.0)	1.0			
College/undergraduate degree	94 (64.8)	1.28 (0.79–2.06)	0.31		
Graduate/professional degree	56 (64.4)	1.25 (0.73–2.19)	0.42		
Ethnicity					
White	116 (58.6)	1.0			
Asian	69 (64.5)	1.28 (0.79–2.10)	0.31		
Black	15 (71.4)	1.76 (0.68–5.13)	0.26		
Other	34 (73.9)	2.0 (1.0–4.24)	0.06		
Sexual orientation					
Gay	200 (61.3)	0.62 (0.31–1.17)			
Other	36 (72.0)	1.0			
No. different STIs ever diagnosed (per 1-unit increase)	—	2.1 (1.7–2.7)	<0.001	1.9 (1.5–2.6)	<0.001
HIV positive	20 (90.9)	6.4 (1.8–40.8)	0.013		
Concern about STI acquisition					
Little to no concern	73 (67.0)	1.0			
More than a little bit concerned	56 (58.9)	0.71 (0.4–1.2)	0.24		
Very concerned	105 (61.4)	0.78 (0.5–1.3)	0.34		
Prior knowledge of PrEP	187 (70.0)	2.90 (1.84–4.58)	<0.001		
Prior knowledge of PEP	146 (72.0)	2.39 (1.57–3.68)	<0.001		
Prior knowledge of HPV vaccine	168 (69.1)	2.21 (1.43–3.41)	<0.001		
Previous use of HIV PrEP	43 (86.0)	4.27 (1.98–10.65)	<0.001	2.9 (1.1–8.3)	0.03
Previous use of HIV PEP	30 (79.0)	2.42 (1.13–5.83)	0.03		
Previous use of HPV vaccine	97 (73.0)	2.05 (1.30–3.27)	0.002		
No. STI prevention technologies previously used	—	2.0 (1.5–2.8)	<0.001		
Currently use HIV PrEP	39 (83.0)	3.30 (1.57–7.81)	0.003		
Disagree with the statement, “The only truly effective means of STI prevention is condom use”	105 (70.0)	1.72 (1.12, 2.69)	0.02		
Depression	29 (82.9)	3.13 (1.35–8.55)	0.01		
Problem alcohol use	149 (61.8)	0.91 (0.59–1.42)	0.69		
Problem drug use	15 (75.0)	1.75 (0.65–5.52)	0.29		

associated with prior knowledge of HIV PrEP, HIV PEP, and HPV vaccination, as well as current/prior use of these STI prevention technologies, with ORs in the range of 2.0 to 4.3 (Table 1).

In the final multivariable model, the only characteristics associated with willingness to use HSV PrEP were the total number of different STIs ever diagnosed (adjusted OR [aOR], 1.9 per STI; 95% CI, 1.5–2.6) and previous HIV PrEP use (aOR, 2.9; 95% CI, 1.1–8.3). Willingness reached 98% in prior PrEP users with a history of 4 different STIs (Supplemental Digital Content 3, <http://links.lww.com/OLQ/A595>).

In exploratory analyses, willingness to use HSV PrEP was strongly associated with willingness to use syphilis PrEP ( $\chi^2 = 104.1$ ,  $P < 0.001$ ) and syphilis PEP ( $\chi^2 = 91.9$ ,  $P < 0.001$ ).

## DISCUSSION

In this 2018 cross-sectional survey of Toronto and Vancouver gbMSM attending sexual health clinics, we found moderately high willingness to use hypothetical HSV PrEP, at 61.8%. Similar to our previous findings on syphilis chemoprophylaxis,<sup>10</sup> this willingness was associated with prior STI burden and HIV PrEP use.

To our knowledge, willingness to use hypothetical HSV PrEP has not been previously assessed. Studies about hypothetical HSV vaccines have suggested similar levels of acceptability, with 69% to 79% of parents indicating willingness to vaccinate their adolescent children.<sup>15,16</sup> Although vaccines are in development, no phase 3 trials have achieved their primary end points.<sup>7</sup> A prior study found that willingness to participate in HSV cure trials was high, ranging from 59.0% to 81.2%<sup>17</sup>; those authors emphasized the significant psychological distress posed by a herpes diagnosis, and the high priority placed on curing HSV among patients. Together, these findings suggest that there is value in pursuing HSV PrEP as a novel prevention strategy.

HIV PrEP trials using topical<sup>18,19</sup> and oral tenofovir suggest that moderately protective HSV PrEP may already be achievable. The Partners PrEP trial found that oral tenofovir disoproxil fumarate (TDF) was associated with a reduction in HSV-2 acquisition (hazard ratio, 0.70; 95% CI, 0.49–0.99;  $P = 0.047$ ),<sup>20</sup> and TDF with emtricitabine reduced the number of genital ulcers in the iPrEx trial.<sup>21</sup> Observational data from HIV/HSV-2 coinfecting individuals found that it does not reduce asymptomatic HSV-2 shedding.<sup>22</sup>

Another potential HSV PrEP agent might be valacyclovir, which prevents transmission to sexual partners when taken by an HSV-positive individual.<sup>23</sup> Although its excellent safety profile and affordability are attractive, observational studies in HSV-2-positive individuals have shown subclinical viral replication despite doses of up to 3 g/d,<sup>24</sup> suggesting that potency may be limited. Combining valacyclovir with TDF may be a promising strategy for further study as PrEP and could harness our observed association between current HIV PrEP use with interest in HSV PrEP.

Our study has limitations. First, participants' responses about hypothetical willingness to use HSV PrEP may not predict future behavior. Our findings may overestimate actual use because participants may have assumed 100% efficacy and because the survey did not mention any adverse effects. Second, our Toronto and Vancouver samples differed with respect to several demographic and clinical characteristics, although the city of recruitment was not a significant predictor of willingness to use HSV PrEP in our final model. Finally, results may not be representative of all gbMSM because we recruited sexual health clinic attendees.

Although bacterial STI prevention in gbMSM has emerged as a particularly high priority,<sup>25</sup> reducing the burden of HSV is also important. We observed considerable interest in HSV PrEP among gbMSM, suggesting that further study is warranted. Assuming

HSV-2 incidence is 7.6/100 person-years,<sup>9</sup> a placebo-controlled trial would require 635 gbMSM per arm to detect a relative risk of 0.5 with  $\alpha = 0.05$  and 80% power. Future studies should address patient preferences (acceptable levels of prevention efficacy, costs, feasibility of combining with HIV PrEP, interest in HSV prevention as a strategy for HIV prevention), willingness to participate in clinical trials, and seroprevalence in candidate study populations.

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