Some Straight Talk about Anal Human Papillomavirus Infection

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(See the article by Nyitray et al, on pages 1498–1508.)

For decades, anogenital human papillomavirus (HPV) research largely focused on viral infection in women, with men only discussed in regard to diagnosis and treatment of penile condyloma. It was not until the past decade that investigators began to look in earnest at the natural history of HPV infection in men. Again, most research focused on genital infections, but increasing rates of anal cancer in men who have sex with men and in immunocompromised individuals shed some light on anal HPV infection in these at-risk populations. Still, studies of anal infection in men who have sex with women (MSW) languished, with many researchers dismissing it as a clinically irrelevant or even potentially dangerous area of investigation, fearing iatrogenically induced viral inoculation during sampling from surrounding perianal skin. As a clinician and scientist who has spent a large part of his career investigating HPV-related diseases, I have heard these arguments countless times at conferences and in peer discussions. I have listened as too many young men with anal condyloma who were referred for treatment recounted stories of clinicians refusing to accept that “true” heterosexual men could develop anal warts. Thankfully, things might finally be changing.

In this issue of the Journal, Nyitray et al [1] present results from the largest (to my knowledge) prospective, multicenter, international trial to look at the prevalence of and risk factors for anal HPV infection in MSW. More than 1300 men from Brazil, Mexico, and the United States were enrolled in the HPV in Men (HIM) study cohort. For this analysis, men who acknowledged recent sexual behavior with another man, those with >12 prior male sexual partners, those who refused intra-anal sampling for HPV with a swab, and those with inadequate samples were excluded, leaving >900 evaluable participants. Samples were tested for 37 HPV types and were considered positive for oncogenic HPV if any of 13 known oncogenic types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66) were present. What the authors of this very important article have shown is that anal canal HPV infection in MSW is not rare; HPV was detected in samples from 12% of participants, with 7% carrying an oncogenic type and 7% carrying a nononcogenic type [1].

Although participants enrolled from the 3 international sites differed in some important ways (eg, men from the United States were younger and more likely to refuse anal sampling), there were no statistically significant differences in rates of infection between countries. Multivariate analysis showed that increased lifetime number of female partners, shorter duration of a relationship, and prior oral or anal sex with a man statistically significantly increased the risk of anal canal infection, whereas being a former smoker was inversely associated with infection. With respect to oncogenic HPV infection, multivariate analysis showed that shorter duration of a relationship and prior history of oral or anal sex with a man increased risk. The authors also found that the presence of an HPV type on the penis or scrotum increased the risk of an anal canal infection >2–3-fold, and men with genital infection with HPV type 16 (HPV-16), the most common oncogenic HPV type found in cancers, had a 5-fold increased risk of anal canal HPV-16 infection [1, 2].

So why is this study important? First and foremost, it should put to rest the myth that only men who have had anal sex can have anal HPV infection; by ex-
tension, it demonstrates that MSW can have anal warts. Although it is possible, as the authors point out, that participants could have lied about the gender of their sex partners, this seems an unlikely explanation, given the large sample size and the fact that men excluded from the analysis because of the number or timing of sexual experiences with male partners had almost 4 times the prevalence of anal canal HPV infection, compared with the analyzed population. If anything, I would argue that the prevalence of anal canal HPV infection is probably higher among the population of MSW, given the strict enrollment criteria, which excluded all men with a history of prior clinical anogenital HPV infection, human immunodeficiency virus (HIV) infection, current drug use or sexually transmitted infection, prior imprisonment, and homelessness—all factors associated with increased risk for infection. Participants also had to be willing to comply with a biannual evaluation for 4 years, which could have artificially selected an overly compliant population [1]. This study also only reports the prevalence of intra-anal HPV infection, whereas in a prior cohort of MSW from 2 US sites the authors identified a 25% incidence of anal and perianal HPV infection [3]. Although it is interesting to look at intra-anal HPV infection alone, perianal infection certainly poses risks of progression to clinical disease and opportunities for transmission.

The Nyitray et al [1] study once again teaches clinicians that a detailed sexual history is critical to properly identify the risk of anal HPV infection. The authors have shown that history of oral or anal sex with another man more than doubled the risk of anal HPV infection. We must ask patients not how they define their sexuality, but what their sexual practices are. Pathela et al [4] showed in a cross-sectional, random-digit-dialing telephone survey of >4000 men in New York City that although 91% of participants identified as heterosexual, >10% had had sex with only men or both men and women during the previous year.

Like all good research, this study has left us with many unanswered questions. Even though >10% of participants had anal HPV infection, we must not draw conclusions that this will translate into clinical disease [1]. This study specifically looked at prevalence of infection, and only grossly visible disease was documented. Moreover, this report represents cross-sectional results, and no conclusions can be drawn about persistence of infection. It is possible that isolated anal canal HPV infection will not translate into clinical disease. But there is also a chance that, given the 7% prevalence of oncogenic anal canal HPV infection, we might see a future increase in anal cancer rates in MSW [1]. Although some medical organizations have weighed in on screening for anal HPV-related disease in at-risk populations, there is no indication from the data presented that screening MSW is indicated [5, 6].

The authors have also shown that although the prevalence of HPV infection did not differ between countries, the types of HPV that were detected differed, with men in the United States having a 4-fold greater prevalence of HPV-16 infection, compared with men from other sites [1]. If enrollment continues, I would hope that the US site makes a concerted effort to enroll a broader age range of men, representative of that seen in Brazil and Mexico, to see if the increased HPV-16 infection prevalence holds. Moreover, there was a marked prevalence of infection with nononcogenic HPV types, and the significance of this finding needs to be determined. Although the authors looked at infections in men from 3 countries, these men were all in the western hemisphere, and there may be striking differences in other populations.

The findings suggest how very easy it must be to transmit HPV between partners. If MSW who deny anal penetration can have intra-anal HPV infection, then we must stop viewing HPV infection as a disease that only promiscuous males and females acquire. The data presented by Nyitray et al [1] reinforce the notion that HPV is probably an unavoidable infection for healthy, sexually active individuals. We must destigmatize this infection and understand how important prophylactic vaccination may be.

Finally, if we are to reduce the risk of HPV infection among MSW, we must understand how infection spreads to the anal canal among a population that denies anal penetration. The authors have shown convincingly that HPV infection at a genital site predisposes an individual to anal canal infection, but no conclusions can be drawn regarding mechanisms of infection. Although HPV transmission can occur through autoinoculation, probably involving the fingers, it is also possible that sexual practices can allow for simultaneous genital and anal infection. Might the anal canal act as a reservoir for HPV infection that could then be transmitted to future partners?

Although Nyitray et al [1] have left us with many unanswered questions, we must applaud them for having the courage to persevere. In so doing, they have advanced a field that many argued did not need advancing. Through this important study, we now know that MSW can contract anal HPV infection and that this is not an isolated phenomenon—rather, it is one that occurs across very diverse populations. That is a major leap forward in our understanding of this pathogen.

References


