# Risk Factors for Genital and Anal Warts in a Prospective Cohort of HIV-Negative Homosexual Men: The HIM Study

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*Objective:* The objective of this study was to determine the prevalence, incidence, and risk factors for genital and anal warts in HIV-negative homosexual men in Sydney.

*Study Design:* The authors conducted a prospective cohort study. Participants were asked whether they had had genital and anal warts at each interview. Details of lifetime sexual contacts and sexual behaviors in the last 6 months were collected.

**Results:** Among 1,427 men recruited, 8.9% and 19.6% reported a history of genital and anal warts at baseline, respectively. Incidence rates for genital and anal warts were 0.94 and 1.92 per 100 personyears, respectively. In multivariate analysis, both incident genital and anal warts were associated with younger age. In addition, incident genital warts was associated with insertive fingering (P trend = 0.018), whereas incident anal warts was associated with insertive fingering (P trend = 0.007) and insertive fisting (P trend = 0.039).

*Conclusions:* Anal warts were twice as common as genital warts. Fingering and other manual sexual practices may be an important transmission route for both.

ANOGENITAL HUMAN PAPILLOMAVIRUS (HPV) infection is one of the most common sexually transmissible infections (STIs) in the developed world. It the United States, it is estimated that 5.5 million new infections occur annually, and 20 million people have prevalent HPV infection.<sup>1</sup> Anogenital warts are the clinically visible manifestation of infection with certain subtypes of HPV, predominantly most commonly types 6 and 11.<sup>2,3</sup> In the United Kingdom, anogenital warts are the most prevalent viral STI diagnosed.<sup>4</sup> In Australia, around 4% of people aged between 16 and 59 years in a population-based survey reported ever having such a diagnosis.<sup>5</sup> Anogenital warts are the most common diag-

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Dr. Grulich sits on the Commonwealth Serum Laboratory and Australasian advisory board for its quadrivalent HPV 6, 11, 16, and 18 vaccine.

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noses in sexual health clinics,<sup>6.7</sup> and treatment can be expensive. It is estimated that the cost directly associated with anogenital warts treatment in the United States is approximately U.S. \$200 million per annum.<sup>8</sup>

A quadrivalent vaccine against HPV subtypes 6, 11, 16, and 18 has recently been approved by the U.S. Food and Drug Administration. Efficacy of the HPV vaccine has been demonstrated for cervical intraepithelial neoplasia and external genital lesions in women. The vaccine also may have the potential to prevent anogenital warts among men, and ongoing clinical trials will yield data on the efficacy of the vaccine in the prevention of anogenital warts in men.<sup>9–11</sup>

Although anal HPV is highly prevalent in homosexual men,<sup>12,13</sup> relatively little is known about the epidemiology of anogenital warts in this population. We determined the prevalence and incidence of self-reported genital and anal warts and associated risk factors in a community-based cohort of HIV-negative homosexual men in Sydney, Australia.

#### **Materials and Methods**

#### *Participants*

Participants were men in the Health in Men (HIM) cohort study recruited from June 2001 to December 2004 as described in detail elsewhere.<sup>14</sup> Briefly, men eligible for inclusion met the following criteria: 1) they reported having sex with other men within the previous 5 years, 2) they lived in Sydney or participated regularly in the gay community of Sydney, and 3) they tested HIV-negative at baseline. Participants were recruited from a variety of community-based settings with only 4% recruited in clinical services. No payment was offered. Signed informed consent was obtained from all participants. Ethics approval was granted by the Human Research Ethics Committee of the University of New South Wales.

# Data Collection

All eligible men underwent annual face-to-face interviews with 6-monthly telephone interviews between these visits. Areas cov-

ered in the questionnaire included lifetime sexual contacts such as number of lifetime male and female sexual partners and detailed sexual behaviors in the last 6 months, including number of regular and casual partners in the last 6 months, and demographic factors.

At each interview, detailed quantitative data on number of episodes of insertive and receptive unprotected anal intercourse (UAI) in the last 6 months was collected separately for regular and for casual partners by HIV status of these partners (negative, positive, or unknown) and, for receptive intercourse, by whether ejaculation occurred.<sup>15</sup> In addition, semiquantitative data (never/ occasionally/often) were also collected for the following sexual practices: insertive and receptive oral sex, anal fingering, anilingus (rimming), fisting, use of dildos, intercrural intercourse (thigh sex), wet and dry kissing, sensuous touching, mutual masturbation, and urolagnia ("water sports"). These data were also recorded separately for regular and for casual partners.

HIV serologic testing (AxSYM HIV Antigen/Antibody Combo; Abbott Diagnostics, Abbott Park, IL) was performed annually to identify HIV seroconverters in the study. Participants were required to test HIV-negative to remain in the cohort. In addition, STI screening was offered annually to consenting participants, including hepatitis B (HBcAb, AxSYM CORE; Abbott Diagnostics) and syphilis serology (enzyme immunoassay; ICE Syphilis; Murex Biotech Ltd., Dartford, U.K.).

Participants reported whether they had ever had genital or anal warts at the baseline interview. At follow-up annual visits, they reported whether they had developed genital or anal warts since the last visit.

#### Statistical Analysis

Statistical analyses were performed using STATA 8.2 (STATA Corp., College Station, TX). The exact binomial method was used to calculate 95% confidence intervals (CIs) for history and incident infection rates. Incidence was calculated among those who reported never having genital or anal warts at baseline. Participants who reported a history of genital warts were not included in the risk factor analysis for incident genital warts, and participants who reported a history of anal warts were not included in the analysis for incident anal warts. Date of onset was estimated to be the midpoint between the annual visit at which the participant reported incident lesions and the previous annual visit. Total person-years (PYs) were calculated as the time from study entry to the estimated date of onset or the last interview for participants who did not develop warts.

Logistic regression was used to identify risk factors associated with a history of warts, and Cox regression was used to identify risk factors for incident infections. Data on a large range of anal, oral, and other sexual practices were examined. Crude and adjusted analyses were performed to identify factors associated with a history of genital and anal warts and incident infections. Odds ratios, hazard ratios, and their corresponding 95% CIs were calculated for these associations. Multivariate logistic regression and Cox regression models were developed to determine risk factors that were independently associated with a history of and incident genital and anal warts. Variables with a P value of less than 0.10 in univariate analyses were considered in multivariate analyses. For incident infections, sexual behaviors were examined separately by regular and casual partners. Demographic factors with a P value of less than 0.10 in univariate analysis were considered to adjust for sexual behaviors with each of regular and casual partners in multivariate analyses.

To further exclude the possibility of confounding by UAI, stratified analyses of risk for incident genital warts were conducted among those who did not report any insertive UAI with casual partners, and for incident anal warts, among those who did not report any receptive UAI with casual partners.

#### Results

Between June 2001 and December 2004, 1,427 participants were enrolled in the HIM cohort. The median age at enrollment was 35 years (range, 18–75 years). The majority (95.2%) of participants self-identified as gay or homosexual.

## Previous Genital and Anal Warts

At baseline, 1,422 (99.6%) participants responded to the question concerning a history of genital and anal warts. Eighty-seven reported they did not know whether they had a history of warts and were excluded from further analyses. Of the remaining 1,335, a total of 119 (8.9%, 95% CI = 7.5–10.6%) reported they had a history of genital warts and 262 (19.6%, 95% CI = 17.5–21.9%) reported they had a history of anal warts. Fifty-three (4.0%, 95% CI = 3.0-5.2%) reported they had a history of both.

In univariate analysis, a history of genital warts at baseline was significantly associated with a higher lifetime number of male partners and a higher lifetime number of female sexual partners (Table 1). A history of anal warts was significantly associated with increasing age, except in men aged over 55. In addition, the participant rating anal intercourse as important to him and a higher lifetime number of male sexual partners and prior hepatitis B infection at baseline (assessed by presence of hepatitis B virus core antibody) were significantly associated with anal warts. Overall, greater gay community attachment was also related to a history of anal warts.

In multivariate analysis, a history of genital warts was associated with a higher lifetime number of both male (P trend <0.001) and female (P trend =0.015) sexual partners. A history of anal warts was associated only with a higher lifetime number of male partners (P trend <0.001), and the association with greater gay community attachment was of borderline significance (Table 2).

#### Incident Genital and Anal Warts

By the end of 2005, 1,245 (87.2%) men completed at least one face-to-face interview, and the total follow-up time was 3,181 PYs. The median follow-up time was 2.3 years. Among those who reported never having genital warts at baseline, 26 reported incident genital warts during the course of the study, giving an incidence of 0.9 per 100 PYs (95% CI = 0.6–1.4). Among those who reported never having anal warts at baseline, 46 reported incident anal warts, giving an incidence of 1.9 per 100 PYs (95% CI = 1.4-2.6).

Incident genital and anal warts were both significantly associated with younger age (Table 3). Compared with those who did not report UAI, those who reported having any UAI with both regular and casual partners, engaging in both insertive and receptive UAI, and having any UAI with HIV-positive partners were significantly more likely to report incident anal warts (Table 3). In contrast, incident genital warts were not associated with UAI. Neither incident genital nor anal warts was associated with number of regular or casual partners in the last 6 months. There was no association between incident genital or anal warts and cigarette smoking. Reporting anal warts previously was not associated with incident genital warts (P = 0.805), and reporting genital warts previously was not associated with incident anal warts (P = 0.619).

A large variety of other sexual behaviors with each of regular and casual partners were examined, including insertive and receptive oral sex, rimming, fingering, fisting, and the use of dildos. Only more frequent insertive fingering with casual partners was significantly

TABLE 1. Univariate Analysis of Risk Factors for Self-Reported History of Genital and Anal Warts at Baseline in the
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	2										0.67-3.16			
											0.83-4.17			

\*Score test for trend of odds.

<sup>†</sup>Test of homogeneity.

OR indicates odds ratio; CI = confidence interval.

associated with incident genital warts (*P* trend = 0.037). Those who reported more frequent insertive fingering (*P* trend = 0.016) or insertive fisting (*P* trend = 0.006) with casual partners were at significantly elevated risk of incident anal warts. The association with frequent receptive use of dildos with either regular (*P* trend = 0.090) or casual (*P* trend = 0.093) partners approached significance.

In multivariate analysis, incident genital warts were significantly associated with younger age (P trend = 0.001) and more frequent insertive fingering with casual partners (P trend = 0.018). Incident anal warts was significantly associated with younger age (P trend = 0.007), more frequent insertive fingering (P trend = 0.039), and insertive fisting (P trend = 0.034) with casual partners. After adjusting for these behaviors, UAI was not significantly related to risk.

In stratified analyses among those who reported no insertive UAI with casual partners, the association between incident genital warts and more frequent insertive fingering with casual partners was of borderline significance (*P* trend = 0.087). Among those who reported no receptive UAI with casual partners, incident anal warts was significantly associated with more frequent insertive fisting with casual partners (*P* trend = 0.010), and the association with more frequent insertive fingering with casual partners was of borderline significance (*P* trend = 0.087).

#### Discussion

Anogenital warts were highly prevalent in this cohort of HIVnegative homosexual men. Anal warts were roughly twice as common as genital warts with around 20% and 10% of men reporting a history, and around 2% and 1% reporting a first episode each year, respectively. A history of genital warts at baseline was significantly associated with a higher number of male and female lifetime sexual partners. In contrast, only a higher number of lifetime male sexual partners was associated with a history of anal warts. Incident infections were more common among younger men. Incident anal warts were associated with UAI and other nonintercourse anal sexual practices such as fingering, fisting, and the use of dildos.

The HIM study was a large-scale prospective cohort study. The sample was primarily community-based. Hence, we believe the data can be considered as broadly representative of gay community-attached HIV-negative men in Sydney.

Anogenital warts and the HPV infections that cause them are highly prevalent in homosexual men. The multicenter AIDS cohort studies (MACS) in the United States showed that 46% of participants reported a history of anogenital warts at baseline.<sup>16</sup> In the recent EXPLORE study of HIV-negative men who have sex with

		Genital Warts		Anal Warts				
	Adjusted OR	95% CI	P Value	Adjusted OR	95% CI	P Value		
Lifetime number of male sexual partners			<i>P</i> * <0.001			P* <0.001		
1–10	1	_		1				
11–50	2.87	0.65-12.70		3.19	1.10-9.24			
51–200	3.61	0.84-15.53		4.23	1.49-12.03			
201–500	5.20	1.21-22.35		6.35	2.23-18.05			
>500	5.87	1.39-24.75		9.43	3.37-26.37			
Lifetime number of female sexual partners			$P^{*} = 0.015$			N/A		
0	1	_						
1	1.19	0.63-2.22						
2–5	1.72	1.09-2.75						
>5	1.70	0.98-2.97						
Gay community attachment			N/A			$P^{*} = 0.067$		
Not at all				1				
Not very				1.46	0.65-3.27			
Somewhat				1.70	0.77-3.75			
Very				1.93	0.85-4.39			

TABLE 2.	Multivariate Analysis of Risk Fact	tors for Self-Reported History of Ger	nital and Anal Warts at Baseline in the HIM Cohort

\*Score test for trend of odds.

OR indicates odds ratio; CI = confidence interval; N/A = not applicable.

men, 26% tested positive to low-risk anal HPV DNA types, including types 6 and 11,<sup>12</sup> although data on warts were not reported.

In our study, a history of anogenital warts was associated with a higher number of sexual partners. Cross-sectional studies have also reported this association in homosexual men in the United States<sup>12,17</sup> and in men recruited in sexual health clinics and men and women in the general population.<sup>18–22</sup> A history of genital warts was associated with both the number of lifetime male and female sexual partners, suggesting that in some homosexual men, genital warts were related to sexual contact with women. Among homosexual men, herpes simplex virus type 2 seropositivity has also been associated with sexual contact with women in this cohort<sup>14</sup> and elsewhere.<sup>23</sup> It is plausible that sexual contact with women may simply indicate a longer sexual career and, therefore, more time of potential exposure to risk factors for warts. In

TABLE 3. Univariate Association Between Age and Unprotected Anal Intercourse and Self-Reported Incident Genital and Anal Warts in the HIM Study

	Incident Genital Warts							Incident Anal Warts					
	PY	n	Incidence (per 100 PY)	HR	95% CI	P Value	PY	n	Incidence per 100 PY	HR	95% CI	P Value	
Age						$P^{*} = 0.006$						<i>P</i> * = 0.018	
<35	1,016.0	19	1.9	1	_		915.5	27	3.0	1	—		
35–44	1,055.5	3	0.3	0.16	0.05-0.54		917.9	12	1.3	0.46	0.23-0.90		
>44	691.0	4	0.6	0.33	0.11-0.97		567.6	7	1.2	0.44	0.19-1.01		
UAI													
By partner type						$P^{\dagger} = 0.858$						$P^{\dagger} = 0.064$	
No UAI	1,075.9	12	1.1	1	_		986.6	14	1.4	1	_		
With regular only	1,077.8	10	0.9	0.84	0.36-1.95		920.0	19	2.1	1.48	0.74-2.95		
With casual only	356.4	2	0.6	0.52	0.12-2.34		293.0	5	1.7	1.26	0.45-3.49		
With both	252.4	2	0.8	0.84	0.19-3.77		201.3	8	4.0	3.26	1.37-7.78		
By position						$P^{\dagger} = 0.960$						$P^{\dagger} = 0.025$	
No UAI	1,075.9	12	1.1	1	_		986.6	14	1.4	1	_		
Insertive only	437.7	5	1.1	1.06	0.37-3.01		379.7	5	1.3	0.96	0.35-2.67		
Receptive only	217.1	0	0.0	_	_		187.1	1	0.5	0.39	0.05-2.97		
Both	1,031.8	9	0.9	0.82	0.34-1.94		847.5	26	3.1	2.25	1.17–4.31		
By partners' HIV status	S					$P^{*} = 0.538$						$P^{*} = 0.098$	
No UAI	1,075.4	12	1.1	1	_		986.1	14	1.4	1	_		
Negative only	1,035.3	9	0.9	0.81	0.34-1.92		877.4	21	2.4	1.74	0.88-3.42		
Some HIV unknown	534.2	4	0.8	0.70	0.22-2.16		443.5	6	1.4	1.00	0.38-2.61		
Some HIV positive	117.4	1	0.9	0.82	0.11-6.33		94.0	5	5.3	3.95	1.42-10.97		

\*P for trend.

<sup>†</sup>*P* for homogeneity.

PY indicates person-years; HR = hazard ratio; CI = confidence interval; UAI = unprotected anal intercourse.

contrast, the association between anal warts and the number of lifetime male but not female sexual partners suggests that anal warts were primarily the result of homosexual contact.

Given the high sexual transmission efficiency of HPV,<sup>24</sup> the linear association between lifetime numbers of male partners and risk of genital and anal warts, which extended to categories of men reporting more than 200 and more than 500 partners, was unexpected. This might suggest different risk factors for anogenital warts and subclinical HPV infection. Based on their anatomic distribution, the physical trauma of sexual intercourse has long been proposed as a factor contributing to the appearance of genital warts.<sup>25</sup> Another hypothesis is that people with warts—presumably with a much higher inoculum—are substantially infectious,<sup>25</sup> whereas those who are clinically latently infected (polymerase chain reaction-positive only) may be less infectious.

Incidence data on anogenital warts in homosexual men are very limited. In the MACS cohort, it was reported that during the course of the study, 10% of men were diagnosed with anal warts by the study examiners.<sup>17</sup> However, there were no data presented on whether those men had a history of anal warts, so a substantial proportion of these might have been recurrent lesions.

Previous cross-sectional studies in sexual health clinics have reported that genital and anal warts are more common in younger men.<sup>19,20,26</sup> Surveillance data in Europe and the United States also demonstrate that the diagnosis of genital warts peaks in 20 to 24 year olds in both sexes.<sup>3</sup> Our study provides the first longitudinal data to support the association between younger age and incident anal and genital warts.

The association between other nonintercourse anal sexual practices such as fingering, fisting, and the use of dildos with anal warts suggests that not only UAI, but other anal sexual practices, may lead to transmission of anogenital warts in homosexual men. Our stratified analyses in men not reporting any insertive UAI with casual partners (for genital warts) or any receptive UAI with casual partners (for anal warts) further strengthened our finding that manual nonintercourse sexual practices were independently associated with incident anogenital warts. It could be postulated that the association between insertive fingering and incident genital warts might be the result of self-inoculation from contaminated fingers contacting the anorectal area of an infected partner. Others have reported hand carriage of HPV in patients with anogenital warts, raising the possibility of transmission by finger–genital contact.<sup>27</sup>

The study relied on participants' self-report to measure the occurrence of genital and anal warts. These reports were not clinically validated; there were no data on biologic evidence of HPV infection or physical examination. Self-reporting of anogenital warts might be insensitive. A cross-sectional survey conducted among men who have sex with men in the United States showed that only approximately one third of participants who were diagnosed with current anogenital warts by a trained examiner reported the presence of warts before examination.16 Thus, it is likely that our study probably underestimated rates of warts. Nevertheless, the correlation with certain sexual risk factors indicates that our data on the site of infections is reasonably accurate. In addition, only a subset of men infected with HPV 6 or 11 would be expected to develop clinically apparent lesions. The factors that cause HPV infection to produce lesions are not well understood, but warts have long been associated with traumatic lesions and scars (Koebner phenomenon), suggesting that more traumatic sexual practices could be a risk factor for warts.28

The current study demonstrates that both genital and anal warts are highly prevalent in HIV-negative homosexual men in Sydney, and incident cases are concentrated in younger men. The range of sexual behaviors associated with incident warts suggests that safe sex—as defined by HIV prevention programs—is likely to be insufficient to prevent infection or lesions. Although condoms have recently been shown to protect women from HPV infection attributable to vaginal intercourse,<sup>24</sup> the greater diversity of sexual practices by homosexual men may be more likely to circumvent the protection offered by condoms. The role of vaccination in the prevention of this expensive and sexually disabling condition requires investigation.

## References

- Cates W Jr. Estimates of the incidence and prevalence of sexually transmitted diseases in the United States. American Social Health Association Panel. Sex Transm Dis 1999; 26:S2–7.
- Dunne EF, Burstein GR, Stone KM. Anogenital human papillomavirus infection in males. Adolesc Med 2003; 14:613–632.
- Partridge JM, Koutsky LA. Genital human papillomavirus infection in men. Lancet Infect Dis 2006; 6:21–31.
- PHLS DHSS&PS and the Scottish ISD (D)5 Collaborative Group. Sexually Transmitted Infections in the UK: New Episodes Seen at Genitourinary Medicine Clinics, 1991 to 2001. London: Public Health Laboratory Service, 2002.
- Grulich AE, de Visser RO, Smith AM, Rissel CE, Richters J. Sex in Australia: Sexually transmissible infection and blood-borne virus history in a representative sample of adults. Aust N Z J Public Health 2003; 27:234–241.
- Donovan B, Mindel A. Are genital herpes and warts really disappearing problems? Aust J Public Health 1995; 19:216–217.
- Kyriakis KP, Hadjivassiliou M, Paparizos VA, Riga P, Katsambas A. Determinants of genital wart case detection rates among STD clinic attendees in Athens, Greece. Int J Dermatol 2005; 44:650–653.
- Insinga RP, Dasbach EJ, Elbasha EH. Assessing the annual economic burden of preventing and treating anogenital human papillomavirusrelated disease in the US: Analytic framework and review of the literature. Pharmacoeconomics 2005; 23:1107–1122.
- Emeny RT, Wheeler CM, Jansen KU, et al. Priming of human papillomavirus type 11-specific humoral and cellular immune responses in college-aged women with a virus-like particle vaccine. J Virol 2002; 76:7832–7842.
- Villa LL. Efficacy of a quadrivalent HPV (types 6, 11, 16, 18) L1 VLP vaccine against external genital disease: A combined analysis. Eur J Obstet Gynecol Reprod Biol 2006.
- Villa LL, Costa RL, 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; 6:271– 278.
- Chin-Hong PV, Vittinghoff E, Cranston RD, et al. Age-specific prevalence of anal human papillomavirus infection in HIV-negative sexually active men who have sex with men: the EXPLORE study. J Infect Dis 2004; 190:2070–2076.
- Palefsky JM, Holly EA, Ralston ML, Jay N. Prevalence and risk factors for human papillomavirus infection of the anal canal in human immunodeficiency virus (HIV)-positive and HIV-negative homosexual men. J Infect Dis 1998; 177:361–367.
- 14. Jin F, Prestage GP, Mao L, et al. Transmission of herpes simplex virus types 1 and 2 in a prospective cohort of HIV-negative gay men: The Health in Men Study. J Infect Dis 2006; 194:561–570.
- Crawford JM, Kippax SC, Mao L, et al. Number of risk acts by relationship status and partner serostatus: Findings from the HIM cohort of homosexually active men in Sydney, Australia. AIDS Behav 2006; 10:325–331.
- Wiley DJ, Grosser S, Qi K, et al. Validity of self-reporting of episodes of external genital warts. Clin Infect Dis 2002; 35:39–45.
- Wiley DJ, Harper DM, Elashoff D, et al. How condom use, number of receptive anal intercourse partners and history of external genital warts predict risk for external anal warts. Int J STD AIDS 2005; 16:203–211.

- Khan A, Hussain R, Schofield M. Correlates of sexually transmitted infections in young Australian women. Int J STD AIDS 2005; 16:482–487.
- Wen LM, Estcourt CS, Simpson JM, Mindel A. Risk factors for the acquisition of genital warts: Are condoms protective? Sex Transm Infect 1999; 75:312–316.
- 20. Svare EI, Kjaer SK, Worm AM, Osterlind A, Meijer CJ, van den Brule AJ. Risk factors for genital HPV DNA in men resemble those found in women: A study of male attendees at a Danish STD clinic. Sex Transm Infect 2002; 78:215–218.
- Van Den Eeden SK, Habel LA, Sherman KJ, McKnight B, Stergachis A, Daling JR. Risk factors for incident and recurrent condylomata acuminata among men. A population-based study. Sex Transm Dis 1998; 25:278–284.
- 22. Habel LA, Van Den Eeden SK, Sherman KJ, McKnight B, Stergachis A, Daling JR. Risk factors for incident and recurrent condylomata acuminata among women. A population-based study. Sex Transm Dis 1998; 25:285–292.

- Mark HD, Sifakis F, Hylton JB, et al. Sex with women as a risk factor for herpes simplex virus type 2 among young men who have sex with men in Baltimore. Sex Transm Dis 2005; 32:691–695.
- Winer RL, Hughes JP, Feng Q, et al. Condom use and the risk of genital human papillomavirus infection in young women. N Engl J Med 2006; 354:2645–2654.
- 25. Oriel JD. Natural history of genital warts. Br J Vener Dis 1971; 47:1–13.
- 26. Hughes G, Catchpole M, Rogers PA, et al. Comparison of risk factors for four sexually transmitted infections: Results from a study of attenders at three genitourinary medicine clinics in England. Sex Transm Infect 2000; 76:262–267.
- Sonnex C, Strauss S, Gray JJ. Detection of human papillomavirus DNA on the fingers of patients with genital warts. Sex Transm Infect 1999; 75:317–319.
- Boyd AS, Neldner KH. The isomorphic response of Koebner. Int J Dermatol 1990; 29:401–410.