



What's Old is New:

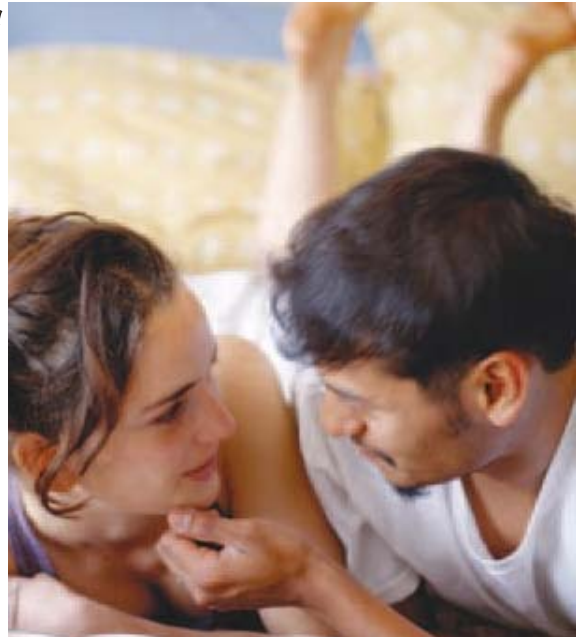
Update on Sexually Transmitted Infections

By Gerald A. Evans, MD, FRCPC

Genital tract infections, chiefly those acquired through sexual transmission, continue to be a frequent cause of visits to primary care physicians. The management of many common genital tract infections has undergone significant change over the last few years. There is now better understanding of the effects of treatment with available antimicrobials, the development of new diagnostic tests, and new compounds with novel modes of action. Finally, the recrudescence of some sexually transmitted infections (STIs) previously in decline warrants the need for physicians to be aware of the ever changing epidemiology of STIs in their communities. This article will focus on a select group of genital tract infections where new information of relevance to practicing clinicians has arisen in the last year.

Is there a new test for Trichomoniasis?

Trichomoniasis is considered the most common non-viral STI worldwide. Although women develop symptomatic infection in most circumstances, men frequently do not. In women, trichomonas vaginitis is associated with an increased risk for the acquisition of human immunodeficiency virus (HIV) and adverse



In this article:

1. How to diagnose trichomoniasis in men and women.
2. What are effective management tools for genital herpes and HPV?
3. What is the importance of rising syphilis rates?
4. How to solve the frustrations of recurrent vulvovaginal candidiasis.

pregnancy outcomes. In men, infection with *Trichomonas vaginalis* usually occurs following sexual contact with infected women and has been associated occasionally with urethritis symptoms.

The diagnosis of trichomonas infection is usually made by microscopy of vaginal secretions in affected women. Culture is the gold standard for diagnosis but requires special media that many microbiology labs do not readily have available. None of these tests are practically applicable to diagnosing infection in men.

Recently, a polymerase chain reactions (PCR) test has been developed for use in men using first-void urine samples.¹ In random field testing at an STD clinic, 24/140 men were positive, giving a prevalence rate of 17%. Women at the same clinic showed a 25% prevalence rate. This test, when available commercially, may be useful in assessing males with culture-neg-

Sexually Transmitted Infections

ative nongonococcal urethritis, or those who are partners of women with recurrent trichomonas vaginitis.

What's new in Genital Herpes?

Genital herpes is the most common ulcerative STI seen by physicians in a general practice. Unfortunately, only 20% of infected individuals present with a classic presentation. Instead, most have no or subclinical signs of infection and frequently unknowingly transmit infection to sexual partners. Data continue to emerge on the growing proportion of herpes simplex virus type 1 (HSV-1) as opposed to HSV-2 related genital herpes. A recent report on 2,343 genital tract isolates from Nova Scotia submitted for viral culture showed 1,266 (54%) were HSV-1.² Rates of HSV-1 isolation were higher in females

age 60, HSV-1 was isolated only 5% of the time. It is thought that the increasing proportion of HSV-1 genital herpes is likely secondary to increasing rates of oral-genital contact, particularly amongst young sexually active adults.

The relevance of this observation lies in the different clinical expression of HSV-1 genital herpes from that associated with HSV-2 genital herpes (Table 1).³ HSV-1 infection in the genital region is associated with less likelihood of recurrent lesions; less frequent recurrences in those who have them; and possibly, a poorer response to antiviral therapy.

Transmission of genital herpes is thought to frequently occur during asymptomatic shedding episodes. Wald and her colleagues showed previously that 65% of patients with HSV-2 shed virus on 1% of all days, and 11% shed on 5% of all days.⁴ Transmission rates are also higher in newly infected individuals and those with frequent recurrences, likely due to heavier viral shedding.

Preventing transmission of genital herpes is more complex than just advocating barrier methods. Evidence supporting condom use as an effective method to reduce transmission of HSV is weak. Condom use is clearly more effective in reducing male to female transmission than female to male transmission, given the difference in anatomical location of genital herpes lesions between men and women.⁵ Viral shedding is shown to be suppressed on antiviral therapy: there is a reduction in the number of days with viral shedding from 6.9% on placebo to

Most patients with genital herpes have subclinical signs of infection, or none at all.

compared with males. In females less than 30 years of age, rates were as high as 71%, while in women over

Table 1

Comparison of HSV-2 and HSV-1 Genital Herpes

Genital Herpes Type	Annual Recurrence Rate	Likelihood of Recurrence	Gender Predilection	Other
HSV-2	6.3 episodes/year	98%	males = females	Higher rates of asymptomatic viral shedding
HSV-1	1.7 episodes/year	<50%	males > females	Less responsive to antiviral therapy?

HSV = herpes simplex virus

Adapted from: Benedetti JK, Zeh J, Corey L: Clinical reactivation of genital herpes simplex virus infection decreases in frequency over time. *Ann Intern Med* 1999; 131:14-20.

0.3% on acyclovir 400 mg orally b.i.d.⁶ With this in mind, investigators now report that this reduction in viral shedding can be translated into a clinically relevant effect on reducing transmission of HSV-2 amongst discordant couples.

Corey et al. reported recently on a randomized, controlled clinical trial of 1,454 monogamous, heterosexual discordant couples at 96 centres worldwide. The trial consisted of 966 infected women and 488 infected men with an average age of 35, whose

Bacterial vaginosis is an independent predictor of HSV-2 infection.

partners were not infected, judging by serology, with HSV-2.⁷ Participants were randomized to either valacyclovir 500 mg daily or placebo for eight months and followed monthly with counselling on how to prevent transmission, condom use, and other methods of prevention. On an intent-to-treat analysis, they showed a significant reduction in seroconversion to HSV-2 positivity (1.9% vs. 3.8% $p = 0.04$, 95% confidence interval (CI) 0.3-0.9). There was also a reduction in laboratory confirmed HSV-2 recovery (0.5% vs. 2.3% $p = 0.006$, 95% CI 0.1-0.7) in the uninfected partner in those couples randomized to antiviral therapy as compared with placebo. This result suggests a benefit to a chronic suppressive antiviral in reducing the likelihood of HSV-2 transmission in motivated, discordant couples who are also counselled regarding this and others methods to reduce viral transmission.



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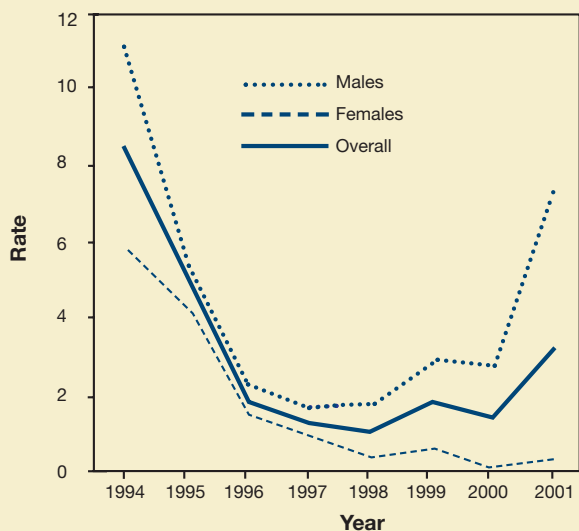
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Sexually Transmitted Infections

Figure 1. Primary and secondary syphilis rates*, by sex and year - New York City, 1994-2001



* Per 100,000 population.

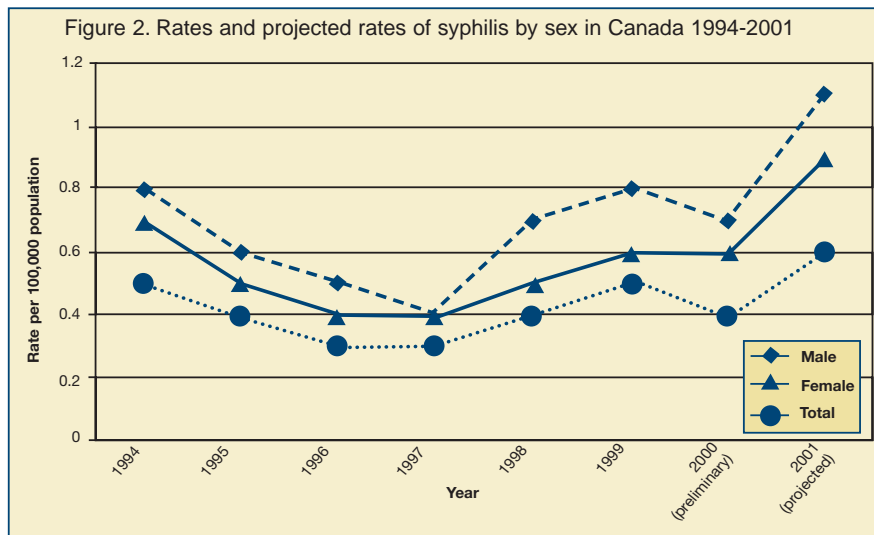
Source: Morbidity and Mortality Weekly Report 2002; 51(38): 853-6.

HSV-2 infection as well (hazard ratio = 2.2, 95% CI 1.0-4.6, $p = 0.04$).⁸ The alterations in normal vaginal microflora seen in BV may have a role in increasing the likelihood of infection with HSV-2 through a yet to be defined mechanism. Finally, genital herpes has been associated recently with an increased risk for HIV infection.⁹ In a case-control study of 116 men who have sex with men (MSM) who seroconverted to HIV compared with 342 HIV seronegative men, a multivariate analysis showed prior HSV-2 infection was an independent predictor of HIV seroconversion (Odds Ratio (OR) 1.8, 95% CI 1.1-3.0).

The Return of Syphilis

Rising rates of primary and secondary syphilis in MSM has been observed in major urban centres in the U.S. since 1998 (Figure 1). This increase has been postulated to arise from a decrease in safer sex practices by MSM and has been correlated with higher rates of HIV co-infection in males infected with *Treponema pallidum*.

In Canada, this has been translated into higher rates and projected rates of syphilis in both men and women (Figure 2). As a result, physicians should be reacquainting themselves with the signs and symptoms of primary and secondary syphilis. They should be increasingly vigilant in assessing sexually active patients presenting with lesions suspicious of a syphilitic chancre and those presenting with unexplained generalized rashes or unexplained alopecia.



Source: STD Epi Update Feb 2002 Health Canada Centre for Infectious Disease Prevention and Control Population and Public Health Branch at http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/epiu-aepi/std-mts/insyph_e.html

The association of genital herpes with other STIs has also been examined recently. Bacterial vaginosis (BV) has been known for years to predispose to lower genital tract infection with *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in women. A recent study now shows that BV is an independent predictor of

lesions suspicious of a syphilitic chancre and those presenting with unexplained generalized rashes or unexplained alopecia.

Physicians should also be aware of the diagnostic workup for primary or secondary syphilis, including the interpretation of syphilis serology. It should be

noted that in incubating and primary syphilis, the fluorescent treponemal antibody, absorbed test (FTA-ABS) is the most sensitive test and becomes positive earlier than the standard screening tests: Venereal Disease Research Laboratory (VDRL) or rapid plasmin reagin (RPR). Direct examination of material from a primary chancre for the presence of treponemes is difficult due to the lack of darkfield microscopes in most clinical laboratories. Any suspicious case of syphilis should be referred to either an infectious disease specialist or a local STD clinic for further evaluation.

The treatment of syphilis continues to be through the use of long-acting depot forms of intramuscular (IM) penicillin. For primary or secondary syphilis, benzathine penicillin 2.4 million units IM once is sufficient. The treatment of later forms of syphilis, in particular late latent syphilis, requires longer duration of treatment. Currently, it is recommended that benzathine penicillin 2.4 million units IM weekly for three weeks be used unless there is a suspicion of neurosyphilis. Central nervous system involvement with syphilis invariably requires further assessment and, if confirmed, a prolonged course of high-dose intravenous penicillin G for successful eradication. Patients with neurosyphilis are best managed by physicians with expertise in syphilis therapy. Recently, the availability of benzathine penicillin has become problematic in Canada due to the manufacturer ceasing its production. Other manufacturers outside Canada will likely fill the void when federal regulatory authorities license their products for distribution.

Is there a new treatment for RVVC?

Recurrent Vulvovaginal Candidiasis (RVVC) affects 5% to 8% of all pre-menopausal women and is defined as four or more culture-proven episodes of vulvovaginal candidiasis per year. Risk factors for RVVC include antibiotic use, oral contraceptive use, increasing sexual activity, douching, diabetes mellitus, HIV infection, and hormonal replacement therapy. Inadequate therapy of acute vulvovaginal candidi-

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The effects of atorvastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol on cardiovascular morbidity, mortality, or total mortality have not been established.

† A patient-year represents the total time of exposure to LIPITOR as defined by the sum of each patient time on LIPITOR.⁵

Sexually Transmitted Infections

Table 2

Comparison of different modalities used in the treatment of genital warts

	Modality	Clearance Rate	Recurrence Rate
Provider-Applied	Surgical Excision	89% to 93%	19% to 22%
	Electrodessication	94%	25%
	CO ₂ Laser	72% to 97%	6% to 49%
	Cryotherapy	70% to 96%	25% to 39%
Patient-Applied	Imiquimod	40% to 77%	13%
	Podofilox	68% to 88%	16% to 34%

Adapted from: Beutner, KR, Ferenczy A: Therapeutic Approaches to Genital Warts. Am J Med 1997;102:28-37.

asis is also a contributor to the prevalence of RVVC. Management of RVVC is problematic and frustrating for many physicians. Recommendations have varied from advocacy of a yeast-free diet, to the use of topical home remedies, such as yogurt douches, vinegar douches, and the topical application of gentian violet.

More recently there has been interest in the use of regular topical or oral anti-fungal azoles, given their reported success in treating acute vulvovaginal candidiasis. Sobel and his colleagues recently reported the results of a randomized double-blind clinical trial in RVVC of oral fluconazole (FCZ) 150 mg weekly versus placebo for six months.¹⁰ The study enrolled 379 patients with RVVC and a mean age of 33.8, where 189 received FCZ, and 190 received a matched placebo after an induction period of three doses of FCZ administered every three days. Of the total group, 94.4% had documented infection with *Candida albicans*. Results showed a statistically significant higher cure rate at the end of therapy (90.8% vs. 35.9%) and at the six-month followup (42.9% vs. 22.1%) in those subjects randomized to fluconazole as compared with placebo. Clinical relapses, however, were higher at six months (31.2% vs. 8.4%) in those

women who received anti-fungal therapy as compared with those on placebo. This study outlines at least one potentially useful management strategy for physicians in treating otherwise healthy women with RVVC caused by *Candida albicans* in whom risk factors for RVVC have been eliminated.

Genital HPV Infection: Is there something new?

Clinical and subclinical genital human papillomavirus (HPV) infection is the most common sexually transmitted infection in the world. Asymptomatic genital HPV infection can be detected in 5% to 40% of women of reproductive age. One per cent of sexually active adults aged 15 to 49 develops genital warts. The highest rate of genital HPV infection is in women less than 25 years of age. Early sexual activity and menarche are associated strongly with acquisition of HPV infection in women.

Approximately 35 of the over 100 known types of HPV can cause infection in the genital region. Genital infection with certain HPV types (16, 18, 31, 33, 35, etc.) has been closely tied to the development of cervical cancer in women and anal cancers in both sexes.

Sexually Transmitted Infections

Genital warts, particularly classic condylomata acuminata, are caused most frequently by HPV types 6,11,42,43,44 and 54. Many laboratories can now assist the clinician in screening HPV isolates collected from patients for high-risk HPV types. Physicians can, therefore, more accurately identify those women who may require closer clinical followup with cervical cytology.

Transmission of genital HPV infection follows direct contact with the virus, usually during sexual contact. Given the location of lesions on the external genitalia, it is often not effectively prevented through condom use. The transformation zone of the cervix is a particular target of HPV infection. Many female patients are found to be infected via typical changes of koilocytosis seen on routine papanicolaou test smears.

Most genital HPV infection resolves over a period of one year, with the exception of patients associated with high-risk HPV types and those with impaired immunity. Patients or their partners most frequently uncover the presence of genital warts. Primary care physicians, however, discover genital warts up to 30% of the time particularly in women during routine pelvic exams. The recognition of genital warts offers the opportunity to counsel patients about risk reduction for HPV and other STIs, and to offer treatment to potentially reduce adverse outcomes and transmission to sexual partners.

Treatments for genital warts can involve provider-applied or patient-applied therapies (Table 2).⁶ Patient-applied therapy is attractive to both the patient and physician as it does not require frequent patient visits for application. A relatively new patient-applied topical therapy, imiquimod, is unique in its mode of action as opposed to previous agents, such as podofilox which work as an antimetabolic agent. Imiquimod is an immune-response modifier which stimulates interferon and other cytokines, and augments the natural immune response to eradicate the wart. Recurrence rates are reported to be slightly lower with imiquimod therapy compared to podofilox. [CME](#)

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Take-home message

- Opportunities to identify infected patients with genital tract infections and their partners, accurately diagnose their infection, and intervene with counselling and appropriate treatment are important for physicians.
- Successful management helps to reduce the public health burden of STIs and improve outcomes for our patients.
- Physicians should maintain their knowledge base in genital tract infection, be aware of published guidelines for managing STIs, and keep up-to-date with important new developments in this changing field of medicine.