Challenges in Genital Herpes Simplex Virus Management

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Development of serologic assays to detect antibodies to herpes simplex virus (HSV) glycoproteins (g)G1 and (g)G2 has allowed accurate definition of the seroprevalence of HSV-2 worldwide. Studies from all continents indicate epidemic proportions of HSV-2 infection. In the United States, 1 in 5 sexually active adults is infected. In Africa and the Caribbean, HSV prevalence is higher. Since the development of the acyclic nucleoside derivatives acyclovir, famciclovir, and valacyclovir, treatment of mucocutaneous HSV is a practice of everyday medical care. Yet, despite effective drugs, there is widespread discontent by clients and providers about care of patients with genital herpes. Much of this relates to transmission complexities and the varied natural history of the infection. However, over time, most patients adjust to their disease and the medical and psychosocial complications. Recent studies show condoms reduce transmission, providing an important tool for counseling the patient with newly diagnosed genital herpes.

Genital Herpes: Patient Management Issues

The number of persons with genital herpes simplex virus (HSV) infections has reached epidemic proportions worldwide, and physicians and patients alike face major challenges in managing the disease and preventing further spread of the virus [1–11]. Many of these conclusions are from seroepidemiologic studies that have used newly developed serologic assays that measure antibodies to glycoprotein (g)G1 and (g)G2, for HSV-1 and HSV-2, respectively. These assays accurately differentiate past HSV-1 from HSV-2 infection, allowing investigators to define the seroprevalence of these infections in a wide variety of populations (table 1) [12–15]. Data from these studies show an ever-increasing trend. For example, in the United States, the prevalence of HSV-2 in the general population is currently 21%, an increase of over 30% since AIDS was discovered [1].

All social strata are affected by the increase in HSV infections. In Europe, contrary to clinical impressions, HSV-2 now is found in 8%–15% of the general population and in 25%–40% of persons with sexually transmitted diseases (STDs) [7, 8, 16–19]. In Africa, the data on HSV-2 prevalence are even more surprising, with prevalence rates of 40%–50% in 20-year-olds despite universal prior HSV-1 acquisition [6, 20, 21] (table 1). Recent seroepidemiologic data from the Caribbean also support high seroprevalence of HSV-2, especially in STD clinic populations (70%–75%). Among human immunodeficiency virus (HIV)-positive populations, seroprevalence rates approach 80% in North America, Europe, and Africa. Thus, there is little doubt that the prevalence of HSV-2 infection has increased greatly in the last 20 years in nearly all countries (table 1).

Antiviral Chemotherapy

While the seroprevalence of infection has increased in the last quarter of a century, so has the physicians’ ability to treat genital herpes. One of the most significant developments of the last 20 years has been development of effective antiviral therapies for the treatment of HSV-1 and HSV-2 [22–27]. The acyclic nucleoside, acyclovir, and the derivative compounds valacyclovir, famciclovir, and penciclovir have revolutionized antiviral chemotherapy [28–33]. These drugs are effective and well tolerated for management of HSV-2 infections; therapy shortens the duration of outbreaks and prevents complications of first-episode infections, such as meningitis and radiculitis. Recent studies show the effectiveness of long-term suppression of HSV in preventing reactivation both clinically and subclinically [34]. Acyclovir is one of the safest oral medications in the prescription drug category. Treatment of genital herpes is now part of the daily routine of the majority of practicing primary care physicians.

Management Is More than Chemotherapy

Despite the generalized use of antiviral therapy, patients and physicians are widely dissatisfied with the care and prevention of genital HSV infections [35–37]. Access to care, treatment, compassionate understanding, and knowledgeable counseling about transmission are often poor and sometimes nonexistent.
Table 1. HSV-2 seroprevalence.

<table>
<thead>
<tr>
<th>Study setting</th>
<th>Persons tested, no.</th>
<th>HSV-2 infection, %</th>
<th>History of genital herpes among persons seropositive for HSV-2, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US population survey, 1990^</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>6407</td>
<td>17.8</td>
<td>9.3</td>
</tr>
<tr>
<td>Women</td>
<td>6687</td>
<td>25.6</td>
<td>9.1</td>
</tr>
<tr>
<td>Family planning clinic (women), Pittsburgh</td>
<td>4527</td>
<td>21.6</td>
<td>12.6</td>
</tr>
<tr>
<td>San Francisco neighborhood survey</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>601</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td>Women</td>
<td>611</td>
<td>41</td>
<td>13</td>
</tr>
<tr>
<td>Other countries b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood donors, London</td>
<td>1325</td>
<td>7.6</td>
<td>19</td>
</tr>
<tr>
<td>Pregnant women, São Paulo, Brazil</td>
<td>655</td>
<td>39</td>
<td>8.2</td>
</tr>
<tr>
<td>Household survey of women, Costa Rica</td>
<td>766</td>
<td>39.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Pregnant women, Sydney, Australia</td>
<td>229</td>
<td>14.5</td>
<td>0</td>
</tr>
<tr>
<td>Pregnant women, Stockholm</td>
<td>1000</td>
<td>33</td>
<td>NA</td>
</tr>
<tr>
<td>High-risk setting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STD clinic, Seattle</td>
<td>776</td>
<td>43</td>
<td>22</td>
</tr>
<tr>
<td>STD clinic, Australia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>80</td>
<td>35</td>
<td>42c</td>
</tr>
<tr>
<td>Women</td>
<td>27</td>
<td>55</td>
<td></td>
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<tr>
<td>STD clinic, London</td>
<td>294</td>
<td>17.3</td>
<td>39.2</td>
</tr>
<tr>
<td>Women</td>
<td>347</td>
<td>24.5</td>
<td>30.1</td>
</tr>
<tr>
<td>STD clinic, Gothenburg, Sweden</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1143</td>
<td>14</td>
<td>30</td>
</tr>
<tr>
<td>Women</td>
<td>475</td>
<td>26</td>
<td>30</td>
</tr>
<tr>
<td>STD clinic, homosexuals, Italy^</td>
<td>783</td>
<td>35</td>
<td>14</td>
</tr>
<tr>
<td>STD clinic, homosexuals, Italy</td>
<td>158</td>
<td>69</td>
<td>14</td>
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<tr>
<td>STD clinic, Lima, Peru</td>
<td>395</td>
<td>83</td>
<td>NA</td>
</tr>
<tr>
<td>Nairobi prostitutes, Kenya</td>
<td>115</td>
<td>61</td>
<td>NA</td>
</tr>
<tr>
<td>Prostitutes, HIV positive, Kinshasa, Zaire</td>
<td>181</td>
<td>95</td>
<td>NA</td>
</tr>
<tr>
<td>Prostitutes, HIV negative, Kinshasa, Zaire</td>
<td>187</td>
<td>75</td>
<td>NA</td>
</tr>
<tr>
<td>Male factory workers, Harare, Zimbabwe</td>
<td>2397</td>
<td>39.8</td>
<td>38.6</td>
</tr>
</tbody>
</table>

^ NOTE: HIV, human immunodeficiency virus; NA, not available; STD, sexually transmitted diseases.

^ From National Health and Nutrition Examination Survey, III.
^ Separate percentage for each sex not available.
^ No difference in HSV-2 seroprevalence in men and women.

In addition, physicians are frequently uncomfortable discussing the complex issues of acquisition and the consequent emotional burdens that genital herpes causes in patients’ lives [38, 39]. Studies of subclinical shedding have identified the risks of potential transmission to partners and the consequence of frequent reactivation for transmission. Most importantly, recent studies have shown clearly that the majority of HSV-2-seropositive persons reactivate virus in the genital area [40–43].

The difficulty in describing the variable patterns of shedding and the vagaries of physicians in communicating risks of transmission to patients make tackling these issues difficult. In addition, the information that medical practitioners must discuss with their patients with HSV-2 may seem alarming: Nearly all (>90%) HSV-2-seropositive persons will shed virus in the genital tract [41]. The frequency of shedding is variable (from 4% of days in some persons to 75% of days in others). There are no predictors of who is a low- versus a high-rate shedder [44].

Shedding is usually asymptomatic, occurring at internal mucosal sites or from unnoticed areas so there is no way to identify when it occurs [43, 45], and shedding rates and reactivation rates decrease over time but the disease changes over 3–5 years rather than over months [46].

Despite these difficulties, there are positive messages about prevention and transmission (table 2). Recent data suggest that the rate of transmission of HSV-2 from an infected person to a susceptible sex partner is higher when sexual activity occurs in the presence of genital lesions [47–49]. Thus, it appears the efficiency of transmission when lesions are present is higher than with subclinical shedding. Of importance, these data suggest that sexually active and HSV-2-seropositive persons should be counseled about the risk of transmitting infection when they have lesions. More recently, a study indicated that consistent use of condoms reduced transmission rates from men to women [50]. While HSV recurrences occurred, when condoms were used during more than 70% of sexual encounters, transmission was reduced by more than 60% [50].

Acyclovir, famciclovir, and valacyclovir markedly reduce viral shedding, including subclinical shedding, as documented by
both culture and polymerase chain reaction (PCR) [34, 44].

Thus, for patients and practitioners, the key question in current therapy is “Can chemoprophylaxis prevent transmission and acquisition?” This question is not easy to answer.

While we remain optimistic that daily antiviral therapy may reduce transmission of HSV from subclinical shedding, we must await clinical trials to define the utility of this approach in clinical practice. Antivirals do not totally abrogate PCR detection of virus [44]. Moreover, maternal-fetal transmission has been documented during episodes of vaginal shedding at delivery when HSV DNA was present but no virus was isolated (PCR positive/culture negative) [51]. Thus, the fact that antivirals do not entirely eliminate PCR positivity introduces uncertainties about recommending antiviral therapy for reducing transmission.

A clinical trial evaluating serodiscordant heterosexual sex partners is currently underway and answers regarding the efficacy of suppressive antiviral therapy for reducing the spread of genital herpes between sex partners should be available during the year 2002. How effectively and for how long such a strategy will work is unclear. One trial, even if successful, always raises questions about “use” or even “abuse” of such a strategy. It is likely that behavioral counseling will still need vigilance and direction even if antivirals are found to be useful.

One issue of interest to patients is the use of antivirals for postexposure prophylaxis. The use of zidovudine and other antiretroviral drugs for postexposure prophylaxis for HIV infection has raised the question of using acyclovir for postexposure therapy for genital HSV infections [52]. Recent data indicate that the rate of HSV-2 transmission is about 5 per 1000 sex contacts [50, 53], similar to the rates for the sexual transmission of HIV. Since acyclovir and its metabolites are activated by virus-induced enzymes, many investigators have hypothesized that these drugs may be useful for postexposure prophylaxis. However, there are no data to answer this question. Moreover, it is difficult to design a trial when the risk of acquisition is low and the potential benefit is not well understood [54]. Therefore, no recommendations for postexposure prophylaxis can be made at present.

**Episodic versus Suppressive Antiviral Therapy**

There is a disparity between patients’ requirements and physicians’ services in the treatment of genital herpes. Many patients desire greater control over their outbreaks and consequently may be more satisfied with a strategy analogous to that used in immunocompromised populations—suppression of reactivation rather than episodic treatment regimens. Several studies have shown that patients’ quality of life is usually better with suppressive versus episodic therapy [55]. Likely, this sentiment relates to a person’s anxiety about transmission of infection to their sex partners. As noted, whether suppression actually alters this perception is unknown. But, despite the desire of patients for chronic therapy, 80% of the courses of antiviral therapy currently prescribed for genital herpes are for treatment of symptomatic episodes (short-course episodic therapy) [55, 56]. This disconnect has led to discontent on both sides of the physician-client aisle.

In the Seattle experience, both forms of therapy are useful to patients and even the same patient over time. Many persons initially “require” suppressive therapy to “cope with the infection” and learn to “live with it” until they become comfortable having a chronic infection, explaining it to their friends and intimates and convincing themselves that they can overcome this illness. During this stage of illness, they are more satisfied and are quite compliant with daily therapy. However, after a period on suppressive therapy, they may decide to switch to episodic management. Virologically, subclinical shedding is highest in the early months after HSV-2 acquisition. Hence, consideration of early suppressive therapy during the 3–9 months after acquisition should be considered and offered to patients more frequently.

In general, patients evolve through a variety of stages during therapy. Most will acquire both a psychological and a physical
equilibrium with their infection. With counseling, they learn to manage their infection by a combination of antiviral therapy, condom usage, and behavior modification and, over time, require only intermittent active management. Moreover, counseling can be more efficient if ancillary materials (e.g., print or web-based materials) are available. The key information outlined in table 2 can be covered in 4–5 min if supplemental materials are provided.

### HSV Infection in HIV-Positive Persons

Another area in which more attention to management is needed is in HIV-infected persons. Recent studies indicate that most HIV-infected persons are HSV-2 seropositive and that HIV-positive persons reactivate HSV-2 on 30%–50% of days [57–61]. Most reactivation is subclinical. Perirectal reactivation is particularly frequent. Chronic suppressive antiviral therapy is effective in abrogating reactivation [56]. The frequency of HSV-2 reactivation is influenced by both CD4 cell count and viral RNA levels [57]. Of interest, highly active antiretroviral therapy does little to reduce HSV-2 mucosal reactivation rates [61]. These data indicate that all HSV-infected persons should be tested for HSV-2 antibodies and that HSV-2/HIV-1–infected persons be considered for HSV antiviral therapy. In most, chronic suppression will lead to better relief from reactivation than intermittent episodic therapy.

### Laboratory Diagnosis

Because HSV-2 is a chronic illness, an accurate diagnosis is essential with laboratory confirmation of the diagnosis when possible. If no visible lesions are present but the patient has a history of recurrent lesions (and there is little risk of chancreoid or *Haemophilus ducreyi* infection), then a serologic assay will provide the most accurate and efficient laboratory confirmation of the infection. The testing laboratory should be requested to provide the results as HSV-1 (g)G1 antibodies present or absent and HSV-2 (g)G1 antibodies present or absent. Cultures should be used for diagnosing first-episode infections since antibodies to (g)G1 or (g)G2 may take 2–6 weeks to develop.

Referral to an American Social Health Association local HELP Chapter (http://www.ashastd.org/hrcl/hselprrp1.html) is an excellent way to assist patients in acquiring first-hand knowledge about their disease. Such organizations have affiliated medical personnel who can provide the depth of contact and time that some patients require. If fundamental treatment of the infection is provided and patients are given access to self-help groups and reputable materials, much can be achieved in managing the infection efficiently and fulfilling patients’ expectations of treatment goals.

### References


