EDITOR'S CHOICE

Herpes complex

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In a blood-red splatter, the word "Herpes" adorned the cover of Time Magazine of 2 August 1982 along with the tagline: "Today's Scarlet Letter". It appeared to herald an era of heightened public interest for herpes simplex virus (HSV) as a "new" sexually transmitted infection (STI). Of course, this attention was quickly overshadowed by increasing awareness of a really new, but much more serious STI: HIV. In the past 25 years, although perhaps less sensational than the progress in HIV research, studies into HSV, especially the genital variant HSV-2, have yielded many important insights that are now leading to renewed efforts to push the prevention of genital herpes to the foreground, inviting the question as to whether aggressive HSV-2 control efforts are now feasible and, from a public health view, warranted.

First, HSV-2 is much more prevalent than was previously thought. Among the general US population, 17% show serological evidence of infection; up to 40% in the African-American subpopulation.[1] The article by Glynn and colleagues[2] (***see p 356***) shows that HSV-2 infection was widely spread in parts of sub-Saharan Africa even before the HIV epidemic and that HSV prevalence over time does not seem to have been strongly influenced by the co-occurrence of HIV.

Second, controlling HSV-2 has been seen as a potentially important tool in HIV prevention because of the ample evidence that HSV-2 is an important co-factor in the acquisition of HIV.[3] Third, control of HSV may reduce the incidence of neonatal herpes, a cause of severe morbidity and mortality.[4] Fourth, antiviral HSV-2 therapy is not only effective in treating symptomatic HSV-2 infections, but also reduces HSV genital shedding[5] and reduces HSV transmission to uninfected partners.[6] With more anti-HSV drugs coming off-patent, these drugs are increasingly affordable. Fifth, type-specific serological tests for HSV are increasingly sensitive and specific and have a high positive predictive value in high prevalence populations.[7] Rapid HSV tests are currently being marketed at prices that will allow them to be considered for routine use in certain clinical settings, for example STI clinics. Finally, clinical trials into preventive HSV-2 vaccines have yielded mixed results thus far[8] and condom use might be only partly effective in preventing HSV transmission.[9] Testing and suppressive treatment for those infected have thus emerged as the mainstay of a possible intervention to prevent the ongoing transmission of HSV.

From a public health perspective, we believe that being able to prevent neonatal herpes and HIV infection are the two consequences of HSV-2 infection that would support the case for a public health intervention including testing and suppressive treatment. Neonatal herpes is an uncommon but very serious condition and everyone will agree that effective prevention is desirable. However, there is insufficient evidence to show that screening and suppressive therapy among men prevent infection in their female partners to the extent that it will prevent neonatal herpes when they become pregnant. Suppressive therapy can reduce but does not eliminate transmission in serodiscordant couples. Furthermore, follow-up time in HSV-2 transmission studies has been relatively short so transmission might simply be delayed in long-standing relationships. This might, perversely, move the time of infection in uninfected female partners to when they can least afford to become infected: pregnancy. There are two additional issues that should be addressed in this context. First, the relationship of genital herpes to neonatal herpes is paradoxical; the risk of transmission is greatest when herpes is acquired during pregnancy and pre-existing herpes is relatively protective,[10] most likely as a result of passive immunity in the fetus from circulating maternal antibody. Therefore, from the view of preventing neonatal herpes, there should probably be a greater focus on preventing transmission during than before pregnancy. Second, a significant proportion of neonatal herpes is caused by the oral/labial HSV-1 variant,[11] so screening and suppressive therapy for HSV-1 would also need to be included in a comprehensive intervention aimed at preventing neonatal herpes.

The well-established role of HSV-2 as a co-factor in HIV transmission and acquisition fostered the exciting possibility that suppressing HSV-2 might help prevent HIV acquisition and transmission and become an important biomedical weapon in the HIV prevention armamentarium. Unfortunately, two recently completed randomised trials among women and men who have sex with men with HSV-2 in Africa, south America and the United States showed that long-term suppressive antiviral therapy with acyclovir did not prevent them from acquiring HIV infection.[12 13] The investigators suggested that the levels of adherence to treatment and perhaps the doses of antiviral drugs required might not be achievable. This does not bode well for the real-world application of such interventions. Trials to demonstrate the potential use of HSV suppression on transmission from HSV/HIV dually infected individuals are still underway, and if shown efficacious may affect the medical management of dually infected patients in the future.

Another potential public health argument for promoting more widespread HSV testing and (suppressive) treatment is that HSV infection per se causes enough psychological and physical morbidity to warrant more aggressive herpes prevention strategies.[14] There is no doubt that HSV-2, particularly primary infection, can cause severe clinical symptoms, especially among women. However, serious manifestations are rare and most people with

Figure 1 Time Inc./Time Life Pictures/Getty Images.

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serological evidence of HSV infection have no or minimal symptoms and do not recall a history of genital herpes.[15] In addition, one has to wonder whether the attention of the medical community to genital herpes and its "scarlet letter" spillovers into the public media enhance the perception in the general public of genital herpes as a serious illness. Measures that elevate genital herpes to the level of a public health priority and urge the public to get tested and treated might thus increase the herpes-associated morbidity and stigma that they aim to prevent.

In the absence of a preventive vaccine, the ethical, programmatic and economic issues about testing and treatment strategies need to be considered. The primary aim of a public health approach to preventing HSV transmission is to reduce transmission to uninfected partners. The success of such an intervention will depend largely on identifying infected partners (screening) and on them adhering to treatment when there is little personal clinical benefit, especially when they themselves are asymptomatic. Patients and their partners should be able to make this decision individually. Pressure exerted by the public, physicians, politicians and public health programmes to encourage medical interventions solely for altruistic purposes has to be resisted until the ethical, economic and epidemiological ramifications have been resolved. There have been no studies to show that such interventions do more good than harm or have any impact on transmission at a population level.

Finally, any expansion of herpes testing and treatment will be expensive. With HSV-2 seropositivity rates of 40% and higher among patients visiting publicly funded sexually transmitted disease clinics in the United States,[16] testing, counselling and potentially even treating patients who test HSV-2 seropositive will have serious logistical and economic consequences that some fear might turn them into "herpes clinics" and may take away resources from the control of other STI.

In conclusion, advances in the epidemiological, clinical, diagnostic and prevention aspects of genital herpes have raised important questions about whether and how to respond with public health interventions. At present, there are too many uncertainties with respect to various facets of HSV disease and the acceptability and effectiveness of large-scale interventions to be able to make rational public health policy decisions.

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