



IPPF Medical Bulletin

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The herpes-HIV link

Sinead Delany

Herpes simplex virus type II (HSV-2) is the most common sexually transmitted infection worldwide. Typically it causes recurrent episodes of sores or ulcers in the genital area; however, as many as 60–80% of those infected with this virus either have no symptoms or do not recognise their symptoms as those of genital herpes.¹ Recent seroprevalence surveys have shown that, in the developing world, HSV-2 infection is much more common than was previously thought.² Moreover, the high rates of infection are not confined to populations at special risk of other sexually transmitted infections; for instance, the prevalence of HSV-2 infection among women attending family planning services in Zambia, Zimbabwe, and South Africa was as high as 60–70%. In both the developing and the developed world, HSV-2 prevalence is generally higher in women than in men, and is strongly associated with increasing age and sexual activity.²

HSV-2 infection and the transmission of HIV

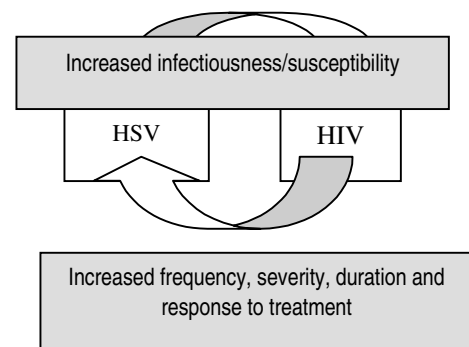
In the developed world, where bacterial causes of genital ulceration are relatively uncommon, HSV-2 has long been recognised as the leading cause of genital ulcer disease. However, it is only in the past decade that, in many countries where syphilis and chancroid were previously endemic, herpes has emerged as the leading cause of genital ulcers.³ Three reasons have been proposed for this apparent change in the epidemiology of genital ulcer disease in the developing world: first, the advent of specific tests based on the polymerase chain reaction has improved diagnosis of genital herpes; second, the introduction in many countries of syndromic management for sexually transmitted infections at primary health care level has led to increased treatment of and a subsequent decline in syphilis and chancroid; and, third (the most likely explanation), coinfection with HSV-2 and HIV has led to worse symptoms and thus more treatment-seeking. HIV infection increases the frequency of HSV-2 reactivation, and the episodes become more extensive and persistent with the decline in CD4+ count. For example, among South African men attending sexually transmitted infection services HSV-2 was detected in 47% of the HIV-positive compared with 28% of the HIV-negative.⁴

Could HSV-2 infection predispose to the transmission of HIV? This possibility is particularly worrying because HSV-2 is the most common cause of recurrent genital ulcer disease in a substantial proportion of the adult population at risk for HIV. The relation between genital ulcers and HIV-1 has been noted since the start of the HIV epidemic. Genital ulcers can be a portal of entry or exit for HIV. In addition,

activated lymphocytes, including CD4 cells, are frequently recruited to these sites of inflammation and are primed to receive or present HIV at the site of ulceration. A meta-analysis of 19 epidemiological studies indicates that prevalent HSV-2 can increase the risk of HIV acquisition in men and women by as much as 3-fold (even after statistical adjustment for sexual behaviour), and that HSV-2 accounts for as many as 38–60% of new HIV infections in women and 8–49% in men in the general populations.⁵

HSV-2 is also thought to enhance HIV transmission from an infected person to an uninfected person. In a study of HIV serodiscordant couples from Uganda, genital ulcers in the HIV-infected partner were associated with a 5-fold increase in per-contact risk of HIV transmission (0.0062 compared with 0.0012 for those without genital ulcer disease).⁶ At the molecular level, HSV-2 has been shown to increase HIV replication through direct effects on HIV transcription.^{7,8} HSV-2 may also enhance HIV replication through indirect mechanisms involving cytokines.⁹ When HIV has been isolated from the genital exudates of persons infected with HSV-2, the HIV RNA levels have sometimes exceeded those measured in the blood;¹⁰ moreover, this excess of HIV in genital secretions has been found even when HSV-2 reactivation is causing no symptoms or clinical signs.^{11,12} Thus, silent reactivation of genital herpes may turn out to be as important as, if not more important than, clinically apparent ulcers in HIV transmission. Figure 1 illustrates the bidirectional relationship between these infections.

Figure 1 Bidirectional and synergistic relationship between HSV-2 and HIV



Antivirals for HSV-2 infection

From the above it is clear that control of HSV-2 might have an important impact on HIV incidence, particularly in settings where HSV-2 prevalence is high. Currently the main option in populations that are uninfected (eg, young people) is primary prevention through condom use, behavioural modification, and promotion of healthy sexual practices. In the future, microbicides may also prove useful in this group to prevent infection with both HSV-2 and HIV. What of antiviral therapy? Several randomised controlled intervention studies are now being conducted in HIV-serodiscordant couples to determine whether treatment of HSV-2 infection lessens the acquisition and transmission of HIV. Table 1

summarises the therapeutic approaches and types of population. Meanwhile, a small study recently reported (February 2006) has added to hope that the large trials will yield positive results. In Burkina Faso 140 women seropositive for both HSV-2 and HIV were randomised to receive either daily valaciclovir (HSV-2 suppressive treatment) or placebo. The valaciclovir reduced the proportion of women with HIV in genital secretions (an index of infectiousness) by 56% and, in those with detectable HIV in genital secretions, the absolute quantity of HIV. An additional observation was that the group receiving active treatment had lesser quantities of HIV RNA in their plasma.¹³

The controlled trials of episodic therapy for HSV-2 reactivation, whether or not they show a lessening of HIV transmission, are likely to yield a public health message by providing further support for the addition of aciclovir to the syndromic management of extensive or persistent genital ulcer disease. Although not curative, the drug does shorten the time to ulcer healing.

Table 1 Questions addressed by HSV-2 treatment trials

Treatment intervention	Population	
	HIV infected	HIV uninfected
Episodic therapy	Does <u>symptomatic</u> genital herpes (ie, genital ulcers) increase HIV transmission?	Does <u>symptomatic</u> genital herpes (ie, genital ulcers) increase HIV acquisition?
Suppressive therapy	Does <u>HSV-2</u> infection increase HIV transmission?	Does <u>HSV-2</u> infection increase HIV transmission?

Anti-HSV-2 strategies for HIV control

Aciclovir is already recommended by the World Health Organization (WHO) as a first-line treatment in countries where HSV-2 prevalence is greater than 30%.¹⁴ For some reason, many such countries have been slow to adopt this policy; the barriers to treatment access at primary health care level need to be identified and surmounted. Daily suppressive therapy with aciclovir has been recommended by WHO for relief of recurrent symptoms of herpes in patients who experience more than six episodes of genital herpes per year. Such treatment, which can reduce recurrences by up to 80%,¹⁵ may be particularly applicable in immunocompromised patients, with their frequent reactivations. But such regimens are likely to be of use only in selected patients with severe genital herpes recurrences. Even if trials of suppressive therapy show benefits in terms of HIV acquisition or transmission, there are doubts about the feasibility of this approach to HIV prevention in general. While these concerns are valid, it will be important not to dismiss out of hand the use of this intervention in selected populations – eg, young women with recent HSV-2 infection to prevent HIV acquisition, or in HIV discordant couples to prevent HIV transmission. Aciclovir is much less expensive than combination antiretroviral therapy (ART) and requires far less in the way of safety monitoring. Although there is good reason to think widespread use of ART might lead to a reduction in HIV transmission, most people who are infected with HIV are in good health at the time of diagnosis and do not require immediate ART. Interventions to reduce HIV transmission in those with CD4+ count greater than 250 are therefore likely to be of benefit to a greater proportion of people than ART, which is generally started when the CD4+ count falls below 250. An intervention that reduced HIV

transmission even in the absence of ART might have great public health impact.¹⁶ The success of these interventions would also give fresh impetus to development of effective HSV vaccines, which could be used in high HSV-2 prevalence settings to stem the tide of HIV transmission.

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Ortho Evra contraceptive patch

Edith Weisberg

Although the combined oral contraceptive pill (COC) is reliable when used correctly, women quite often miss pills in a cycle and thus risk unwanted pregnancy. For such women, the chance of user failure might be lower with a hormonal method that demands less frequent user action, and two of the newer long-acting preparations are a vaginal ring (Nuva Ring) and a transdermal contraceptive patch (Ortho Evra). I reviewed the Nuva Ring in the September 2005 *Bulletin*. Here I discuss the patch.

Ortho Evra, dimensions 4.5 x 4.5 cm, delivers a continuous systemic dose of norelgestromin (NGMN, active metabolite of norgestimate) 150 µg and ethinyl estradiol (EE) 20 µg per 24 hours.¹ The outer layer is a pinkish polyester film that provides structural support and protects the adhesive layer which contains the hormones. The third layer, a transparent film, is removed just before application. Ortho Evra can be applied to any area other than the breast: the manufacturers recommend abdomen, buttock, upper outer arm, or upper torso, and in practice women seem to favour the buttocks. The administration schedule is based on a 28-day cycle, with a patch being applied weekly for three weeks on the same day each week followed by one week patch-free. Data on the patch come mainly from three pooled open-labelled trials in 3319 women who used the method for up to thirteen cycles and from two comparative studies with oral contraceptives.²⁻⁴

Pharmacokinetics and metabolism

The mode of action of the transdermal contraceptive patch is similar to that of COCs, inhibiting ovulation, altering cervical mucus to impede sperm penetration into the uterus, and changing the endometrium to reduce the likelihood of implantation.⁵ After initial application, both NGMN and EE are rapidly absorbed, reaching a plateau in the serum by about 48 hours. Effective serum levels are maintained for 10 days with each patch, allowing 2 days of leeway for users who forget to change the patch. Pharmacokinetic studies^{6,7} indicate that the serum concentrations of both NGMN and EE are lowered slightly by increasing age, body weight, and body surface area. Mean values of follicle-stimulating hormone, luteinising hormone, and oestradiol are suppressed during therapy and return to near baseline about six weeks after cessation. The first-pass metabolism that occurs with COCs (via the gastrointestinal tract, liver, or both) is avoided by transdermal application. Thereafter, NGMN is highly bound to serum proteins, including albumin but not sex hormone binding globulin. EE is extensively bound to serum albumin. The metabolites of both are eliminated in urine and faeces.

A recent observation, which necessitated a change in labelling of the product in the USA, is that users are exposed to about 60% more of the oestrogen component than they would be from a 35 µg COC.⁸ The implications are at present uncertain – see under Adverse events. In previous studies the effects on lipids closely resembled those of COCs (an unfavourable rise in LDL offset by a favourable rise in HDL, together with an increase in triglycerides⁹); nor did patch users show any obvious differences in haemostatic indices. Concomitant use of drugs that affect liver enzymes such as rifampicin and certain anticonvulsants may reduce efficacy.

User experience

In clinical trials, perfect use of the patch – ie, 21 consecutive days of use followed by a 7-day patch-free interval, with no patch worn for more than seven days – was achieved in 90% of cycles. Furthermore, correct use improved over time, from 88% in cycle three to 94% in cycle eight. In the comparative

trials, rates of correct use were higher with the patch than with COCs (88% versus 78%). Women under 30 years of age had the lowest rates of correct use for the COC (68% and 75% for ages 18–19 and 20–24 respectively).¹⁰ In typical use of the patch the pregnancy rate was 0.88%. Pregnancy was more common in women who weighed 90 kg or more, so the patch may be less suitable for such women. Complete or partial detachment of the patch may affect efficacy but complete detachment was reported in only 1.8% of 70 554 patches used and partial detachment in 2.9%. The detachment rate was not increased by humid climates, vigorous exercise, saunas, or bathing.¹¹ (If a patch becomes partly detached it should be removed and reapplied. If it does not adhere fully a new patch is needed immediately. This will change the patch application day as subsequent patches will then be applied on the same day of the week as the replacement patch. Back-up contraception is required for 7 days if the patch has been detached for more than 24 hours).

Cycle control with Ortho Evra is good, with a withdrawal bleed usually starting on day 4 of the patch-free week and lasting 5–6 days. This is on average one day later in onset and one day longer in duration than a typical COC withdrawal bleed and extends into the next patch cycle. In clinical trials 26% of women per cycle had 7 or more total days of bleeding and/or spotting (including both withdrawal and breakthrough bleeding and/or spotting). Spotting occurred more frequently in patch users than in COC users in the first two months of comparative clinical trials (18.3% vs 11.4% in cycle one and 10.0% vs 8.8% in cycle 2).³ There is also some information on continuous use: in a recent study 239 women were randomised to use patches either for twelve continuous weeks or in the 21/7day regimen.¹² In the extended-use group the median number of bleeding/spotting days and episodes was significantly less and the time to the first bleed significantly greater; therefore, this could be an option for women who prefer a more bleed-free regimen.

Adverse events and acceptability

Data on the risk of thromboembolism with Ortho Evra are conflicting. One study, reported in full, has shown no significant difference between patch users and COC users;¹³ but preliminary findings from another point to a two-fold increased risk with the patch.¹² Further studies on this matter, and its possible relation to the higher oestrogen exposure, are underway. Meanwhile, the stated contraindications are the same as those for COCs. In clinical trials the most frequent adverse events leading to discontinuation (in 1.0% to 2.4% of women) included nausea and/or vomiting, application-site reaction, breast symptoms, headache, and emotional lability. Overall, nausea and/or vomiting occurred in 17% of participants, application-site reaction in 17%, breast symptoms in 22%, headache in 21%, dysmenorrhoea in 10%, and abdominal pain in 9%. Breast symptoms were more frequent in patch users than in COC users in the first three months of use but were described by the women as mild (40%) or moderate (50%).

In a multicentre comparison, the continuation rate for the patch was 80% and for a COC somewhat higher at 86%, but a greater proportion expressed satisfaction with the patch than with the COC. The colour and opacity of the patch make it very noticeable but do not seem to lessen its acceptability. Women, especially those over 34 years, rated their emotional and physical wellbeing and their premenstrual symptoms better during their last patch cycle than before participation in the study.¹⁵

Two small studies have assessed use of the patch amongst adolescents.^{16,17} Both found that most adolescents were satisfied with the method, had excellent cycle control, and would recommend it to friends. However, detachment rates

were high – complete or partial detachment reported by about one-third of users.

Conclusion

The contraceptive patch offers an additional choice for women who wish to try a combined hormonal method that requires less frequent action than the COC. The reported satisfaction rates are high. Oestrogen exposure is higher than with the COC and one study, not yet reported in full, has shown a higher risk of venous thromboembolism. Other unwanted effects are similar to those of COCs after the initial two months of use, apart from the specific problems of skin irritation and detachment.

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Fulfilling Fatherhood: Experiences from HIV Positive Fathers

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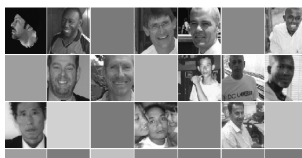
The contributors are unusual in having chosen to speak out about their HIV status and the complex dilemmas it poses. More openness, they say, breaks down barriers.

A recurrent theme is the duty to survive and educate.

Fulfilling Fatherhood shows how, with more information and support, HIV positive fathers can live healthier lives and contribute more to the welfare of their children and families.



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