

## HIV transmission and sexually transmitted infections

Phillip Hay MBBS FRCP, Reader in Genitourinary and HIV Medicine, St George's Hospital, University of London

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HIV is a sexually transmitted infection (STI) which causes AIDS and death in most of those infected after a median of 8–10 years. Where antiretroviral therapy is available, HIV is now regarded as a manageable chronic condition. Prevention remains a high priority and the potential to reduce the number of those acquiring HIV through better control of STIs remains tantalising. This article will review the evidence that STIs are important cofactors for HIV transmission and acquisition.

HIV itself is sexually transmitted so it is often difficult to exclude confounding from observational studies.<sup>1</sup> The time sequence of infections cannot be ascertained easily in cross-sectional studies so longitudinal studies are required. Studies of the effect of STIs on genital tract shedding of HIV provide biological plausibility for mechanisms to associate increased transmission from those with STIs. Randomised controlled studies (RCTs) of the impact on HIV seroconversion rates of interventions to control other STIs are the best measure of their importance.

### Key Points

**Sexually transmitted infections (STIs) are risk factors for both HIV transmission and acquisition**

**There is limited evidence from randomised controlled trials that control of STIs reduce HIV incidence at a population level**

**KEY WORDS:** HIV incidence, HIV transmission, sexually transmitted infections

### Observational studies

Genital ulcer disease from herpes, syphilis and chancroid was identified early as an important risk factor for HIV acquisition in men (both homosexual and heterosexual) and heterosexual women. A study in 1983–1986 into the cause of proctitis in 200 homosexual men found that infection with HIV was independently associated with a history of syphilis, serologic evidence of syphilis, a history of herpes simplex virus (HSV) infection and antibody to HSV-2.<sup>2</sup>

A prospective study in Nairobi of 422 men who acquired STIs following sex with female commercial sex workers (CSW), 85% of whom were seropositive,<sup>3</sup> found that newly acquired HIV infection was significantly associated with the acquisition of genital ulcer disease (relative risk (RR) 4.7) and with being uncircumcised (RR 8.2). The frequency of HIV-1 infection in a subgroup of 73 seronegative men who reported a single prostitute sexual contact was 8.2% during 12 weeks of observation. No man without a genital ulcer seroconverted, whereas 43% of uncircumcised men who acquired an ulcer seroconverted to HIV-1 after a single sexual exposure.

Another study from Nairobi looked at risk factors for seroconversion in 124 seronegative female CSWs, 83 (67%) of whom seroconverted.<sup>4</sup> Genital ulcers (mean annual episodes 1.32 in seroconverting women vs 0.48 in seronegative women) and *Chlamydia trachomatis* infections (odds ratio (OR) 3.6) were associated with HIV infection. Stepwise logistic regression analysis confirmed independent associations between HIV-1 infection and oral contraceptive and condom use, genital ulcers and *C. trachomatis*.

Another study of 431 female CSWs in Kinshasa reported adjusted ORs for HIV seroconversion of 4.8 for gonorrhoea, 3.6 for chlamydial infection and 1.9 for trichomoniasis.<sup>5</sup> Genital ulcers were more frequent in cases than controls but much less common than other STIs.

### Genital tract HIV shedding

Viral load correlates with the risk of transmitting HIV. Biological plausibility of the

hypothesis that STIs are cofactors for transmission was provided by studies of HIV levels in the genital tract before and after treatment for STIs. RNA concentrations were measured in seminal and blood plasma from 135 HIV-1-seropositive men in Malawi (86 had urethritis and 49 controls without urethritis).<sup>6</sup> The seminal plasma concentrations were eight times higher in men with urethritis ( $12.4 \times 10^4$  vs  $1.51 \times 10^4$  copies/ml), despite similar CD4 counts and blood plasma viral RNA concentrations. Gonorrhoea was associated with the greatest concentration of seminal HIV-1 in semen ( $15.8 \times 10^4$  copies/ml). After antimicrobial therapy the seminal plasma HIV-1 RNA concentration decreased significantly to  $8.91 \times 10^4$  copies/ml at one week and  $4.12 \times 10^4$  copies/ml at two weeks. Blood plasma viral RNA concentrations did not change.

Among 609 HIV-1-seropositive women in Abidjan, Côte d'Ivoire, HIV-1 shedding was significantly more frequent in immunosuppressed women and those with gonorrhoea (adjusted odds ratio (AOR) 1.9), chlamydia (AOR 2.5) and a cervical or vaginal ulcer (AOR 3.9).<sup>7</sup> HIV-1 shedding decreased from 42–21% ( $p < 0.005$ ) in women whose STI was cured.

Bacterial vaginosis (BV) is not regarded as an STI, but it is a genital infection and has been associated with elevated levels of pro-inflammatory cytokines and reduced levels of protective molecules such as secretory leukocyte protease inhibitor and immunoglobulin A, which might affect susceptibility to HIV. The strongest observational data linking BV with HIV acquisition is from the study of 1,196 HIV-1 seronegative pregnant women in Malawi. BV was significantly associated with both antenatal (AOR 3.7) and postnatal (AOR 2.3) HIV seroconversion.<sup>8</sup>

### Community level sexually transmitted infection interventions

The observations discussed above led to the hypothesis that interventions to reduce the prevalence of STIs would reduce the incidence of HIV. Potential interventions at a community-level included campaigns:<sup>9</sup>

- to promote safer sex
- to improve STI treatment-seeking behaviour
- to improve STI treatment services (attitudes of care providers, case management and contact treatment)
- for the integration of STI case findings in family planning and antenatal care services
- STI screening programmes
- mass treatment of whole communities for STIs.

Several large RCTs (discussed below) were undertaken to investigate whether controlling STIs can reduce the incidence of HIV in a community. Such studies need to establish whether the intervention has reduced both the incidence/prevalence of STIs and the incidence of HIV infection.

### *Mwanza, Tanzania*

Twelve communities (ca 1,200 evaluable adults) and their associated primary care clinics were randomised.<sup>10</sup> Baseline HIV prevalence was 3.8% and 4.4% in the intervention and control communities, respectively. The control communities had no additional interventions. Intervention communities received improved syndromic STI case management comprising:

- establishing an STI reference clinic in the district
- staff training
- regular supply of basic drugs
- regular supervision of clinic staff
- STI health education.

There was a reduction in syphilis and symptomatic urethritis in the intervention group. The incidence of HIV infection was 1.2% and 1.9% in the intervention and control groups, respectively (OR 0.58, 95% confidence interval (CI) 0.42–0.70), corresponding to a 38% reduction (95%CI 15–55%) in the intervention group.

### *Rakai, rural Uganda*

Following this initial positive study two subsequent studies in rural Uganda failed to demonstrate reductions of HIV. The

first was a randomised controlled community-based trial in Rakai of home-based mass antibiotic treatment.<sup>11</sup> Intervention treatment with azithromycin, ciprofloxacin, and metronidazole was compared with control communities receiving vitamins and antihelminthic drugs, administered every 10 months to all consenting adults (15–59 years). An open cohort was used to incorporate newly arrived residents at each study round (total subjects 12,726). More than 80% of eligible adults received treatment. The baseline prevalence of HIV-1 infection was 15.9%. The study was stopped after three of the planned five treatment courses because of the lack of effect found in a planned interim analysis. At 20-month follow-up, the prevalence of syphilis (5.6% vs 6.8%, RR 0.80) and trichomoniasis (9.3% vs 14.4%, RR 0.59) was significantly lower in the intervention groups than in the controls. The incidence of HIV-1 infection was 1.5 per 100 person-years in both groups.

### *Masaka, rural Uganda*

In the second study all adults living in 18 communities in the Masaka district were randomised into three groups.<sup>12</sup> It included 12,819 from a total population of 96,000 aged 13 and older. The aim of the study was to examine the role of behavioural interventions alone, or in combination with improved management of STIs, in reducing the incidence of HIV-1 and other STIs:

- Group A: behavioural interventions alone.
- Group B: behavioural and STI interventions.
- Group C (controls): the routine government health services.

The incidence rate ratio (IRR) of HIV-1 was 0.94 (p=0.72) in group A and 1.00 (p=0.98) in group B compared with group C; the prevalence ratio of condom use with last casual partner was 1.12 (95%CI 0.99–1.25) in group A and 1.27 (95%CI 1.02–1.56) in group B. HSV-2 incidence was lower in group A than in group C (IRR 0.65, 95% CI 0.53–0.80) and both incidence of active syphilis and prevalence of gonorrhoea were lower in

group B than in group C (syphilis incidence RR 0.52, gonorrhoea prevalence ratio 0.25). There was an increase in condom use in all three arms.

### *Rakai, rural Uganda*

In an additional study in Rakai, the effect of the treatment on pregnant women was studied.<sup>13</sup> There were reductions in STIs: trichomoniasis (RR 0.28), BV (RR 0.78), gonorrhoea and/or chlamydial infection (RR 0.43) and adverse pregnancy outcomes such as early neonatal mortality (RR 0.83, 95%CI 0.71–0.97). There was no reduction in incidence of HIV or syphilis.

## Review of intervention studies

The conclusion from a review of the intervention studies by the Cochrane collaboration was that there is limited RCT evidence that STI control is an effective HIV prevention strategy.<sup>9</sup> There was, however, recognition of a benefit in Mwanza which has an emerging HIV epidemic (low and slowly rising prevalence) and where STI treatment services are poor and STIs highly prevalent. Both the Masaka and Rakai studies demonstrated no benefits from mass treatment of populations. The proportion of HIV seroconversions attributable to symptomatic cofactors in the Rakai setting was modest. The symptom most consistently associated with HIV risk was genital ulcer disease, which was mainly caused by incurable HSV-2 or other non-STI pathogens.

## Possible hypotheses to explain the different trial findings

Several hypotheses have been suggested to explain the contrasting results of the Mwanza, Rakai and Masaka trials.<sup>1,14,15</sup> Curable STI probably played a more important role in HIV transmission in Mwanza than in the other two communities. The epidemic in Uganda was more mature and generalised than in Mwanza, with different transmission dynamics. In Rakai, HIV-1 infection was more prevalent than most other STIs.

Further analyses from Rakai show that HIV-1 viral load was the main determinant of transmission risk, and suggest that in discordant couples the effect of viral load on transmission is substantially greater than that of STI symptoms in either partner.<sup>16</sup> Genital herpes is now thought to be the most important cofactor in mature epidemics and was not affected by the treatments in Rakai where HSV-2 was detected by PCR in 45% of genital ulcers. BV is an additional risk factor for which the Rakai intervention did not make a significant long-term reduction.

Untreated symptomatic STIs may have a greater cofactor effect on HIV-1 transmission than symptomless infections, since symptomatic STIs are likely to be associated with a greater degree of inflammation. In Rakai, only limited services were available to treat symptomatic STIs between rounds of mass treatment. Substantial STI prevalence was seen at the end of each 10-month follow-up period, suggesting a high rate of infection and reinfection after mass treatment in this open cohort.

The population-attributable fraction of HIV-1 infections due to STIs varied. In Rakai, only 10% of new HIV-1 infections were attributable to STI symptoms or treatable STIs, and there was no significant difference between intervention and comparison groups. By contrast, in Mwanza 43% of new HIV-1 infections among men in the comparison group could be attributed to symptomatic STIs or new episodes of syphilis compared with 11% in the intervention group.

## Herpes suppression

### Aciclovir

Genital herpes has emerged as an important potential risk factor for HIV transmission. In Tanzania, Watson-Jones *et al* tested the hypothesis that suppressing herpes with aciclovir 400 mg twice daily would reduce the rate of acquisition of HIV in HSV-2 antibody-positive women.<sup>17</sup> This is the first study to test whether a continuous antiherpes regimen reduces the risk of contracting HIV in people already infected with genital herpes.

There was no difference in HIV infection rates among the 821 women enrolled (aciclovir vs placebo RR 1.12). Adherence to treatment appeared to be poor. Intriguingly, a subgroup analysis of those who took more than 90% of their pills showed a lower HIV incidence rate: 2.5 vs 4.3 per 100 person-years (RR 0.58, 95%CI 0.3–1.4), but the numbers were too low to reach statistical significance. The choice of agent may have been important.

Another Tanzanian study explored the potential for aciclovir to reduce genital HIV or HSV-2 shedding in 383 HIV-positive/HSV-2-positive coinfecting women.<sup>18</sup> At baseline, 53% had HIV detectable in their genital secretions and 14% had HSV-2. At six and 12 months, women taking aciclovir had a trend to lower genital shedding of HIV (OR 0.83, 95%CI 0.56–1.26). When the investigators excluded women who had blood or semen in their lavage, the relationship strengthened between aciclovir use and lower genital shedding of HIV (OR 0.64, 95%CI 0.39–1.04) but remained non-significant. Again, only about half the cohort took more than 90% of their treatment. There was also no significant effect on HSV-2 genital shedding.

### Valaciclovir

Whether use of a more potent agent such as valaciclovir and improved adherence would produce more positive results needs to be tested. A study of valaciclovir has shown a more impressive effect on genital tract viral shedding. In Burkina Faso, HSV-2/HIV-1 seropositive women not eligible for antiretroviral therapy were randomised to valaciclovir 500 mg twice daily or placebo.<sup>19</sup> There were 136 evaluable subjects in each arm, with mean CD4 count of 446 cells/mm<sup>3</sup>. There was a significant decrease in the frequency of genital HIV-1 RNA (OR 0.41) and in the mean HIV viral load (−0.29 logRNA/ml) in the valaciclovir arm. HSV suppressive therapy also reduced the mean plasma HIV-1 RNA level by 0.53 logRNA/ml. Significantly fewer women in the valaciclovir group shed HSV-2 (19.1% vs 54.4%, RR 0.35). The proportion of women with at least one genital ulcer sim-

ilarly declined from baseline in the valaciclovir group, from 29.4% in the baseline phase to 4.4% in the treatment phase, as compared with no change in the placebo group (RR 0.16).

## Conclusions

There is no doubt that STIs are risk factors for both HIV transmission and acquisition. The relative contribution of individual STIs to an epidemic varies at different times and places depending on the maturity of the epidemic and their relative prevalence. The disappointing results of the mass treatment studies show that, although improved STI control is not the solution, it can make an impact, as shown in the Mwanza study. Similarly, the biological plausibility that suppressing genital herpes needs further testing. Whatever the outcome of such studies, controlling STIs can still have an impact on morbidity. Additionally, although the pregnancy study in Rakai did not show a reduction in HIV acquisition, there were reductions in adverse pregnancy outcomes such as neonatal mortality.<sup>13</sup>

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