

Review

From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection

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Objectives: To review the scientific data on the role of sexually transmitted diseases (STDs) in sexual transmission of HIV infection and discuss the implications of these findings for HIV and STD prevention policy and practice.

Methods: Articles were selected from a review of Medline, accessed with the OVID search engine. The search covered articles from January 1987 to September 1998 and yielded 2101 articles. Methods used to uncover articles which might have been missed included searching for related articles by author, and combing literature reviews. In addition, all abstracts under the category "sexually transmitted diseases" from the XI and XII International Conferences on AIDS (Vancouver 1996 and Geneva 1998) and other relevant scientific meetings were reviewed. Efforts were made to locate journal articles which resulted from the research reported in the identified abstracts. All original journal articles and abstracts which met one of the following criteria were included: (1) studies of the biological plausibility or mechanism of facilitation of HIV infectiousness or susceptibility by STDs, (2) prospective cohort studies (longitudinal or nested case-control) which estimate the risk of HIV infection associated with specific STDs or STD syndromes, or (3) intervention studies which quantitate the effect which STD treatment can have on HIV incidence.

Results: Strong evidence indicates that both ulcerative and non-ulcerative STDs promote HIV transmission by augmenting HIV infectiousness and HIV susceptibility via a variety of biological mechanisms. These effects are reflected in the risk estimates found in numerous prospective studies from four continents which range from 2.0 to 23.5, with most clustering between 2 and 5. The relative importance of ulcerative and non-ulcerative STDs appears to be complex. Owing to the greater frequency of non-ulcerative STDs in many populations, these infections may be responsible for more HIV transmission than genital ulcers. However, the limited reciprocal impact of HIV infection on non-ulcerative STDs and the evidence that non-ulcerative STDs may increase risk primarily for the receptive partner (rather than bidirectionally) may modulate the impact of these diseases. The results of two community level randomised, controlled intervention trials conducted in Africa suggest that timely provision of STD services can substantially reduce HIV incidence, but raise additional questions about the optimal way to target and implement these services to achieve the greatest effect on HIV transmission.

Conclusions: Available data leave little doubt that other STDs facilitate HIV transmission through direct, biological mechanisms and that early STD treatment should be part of a high quality, comprehensive HIV prevention strategy. Policy makers, HIV prevention programme managers, and providers should focus initial implementation efforts on three key areas: (i) improving access to and quality of STD clinical services; (ii) promoting early and effective STD related healthcare behaviours; and (iii) establishing surveillance systems to monitor STD and HIV trends and their interrelations.

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Introduction

As the interrelation between human immunodeficiency virus (HIV) infection and other sexually transmitted diseases (STDs) has become increasingly well understood, the need to translate these scientific findings into sustainable prevention programmes and policy has become increasingly urgent. In fact, recent evidence that, at a community level, STD treatment can substantially decrease HIV incidence has compelling implications for both STD and HIV prevention, and argues for improved coordination between these often separate efforts.

Recent developments have added complexity and urgency to this topic. For example,

technological innovations have made widespread STD screening and treatment easier and more effective, both in industrialised and developing countries. In the United States and several other countries, the epidemiology of HIV itself is changing, with heterosexual transmission accounting for larger proportions of new infections and affecting increasing numbers of women. Furthermore, the advent of new HIV therapies, which promise to transform HIV infection into a "chronic disease," may have already begun to change perceptions about the importance of maintaining safe sexual behaviours.¹ Finally, new health services research has documented the inadequacy of

existing STD prevention capacity in the United States, as well as most of the developing world.²⁻⁴ Clearly, additional approaches to preventing HIV infection are now feasible and necessary.

With these issues in mind, we will review the scientific foundation for our understanding of the role STDs play in facilitating sexual transmission of HIV, focusing on data from studies published since 1990. We will then discuss the implications of these findings for HIV and STD prevention policy and practice by highlighting initial steps in activities such as community based behavioural intervention, surveillance, and clinical services that would help build truly synergistic HIV and STD prevention programmes.

Evidence defining the contribution of other STDs to sexual transmission of HIV infection

Recent conceptual and empirical work has underlined the reciprocal relation, or "epidemiological synergy," between HIV infection and other STDs, by which each may alter the transmission or manifestations of the other, resulting in a potentially explosive, mutually reinforcing spiral of infection.⁵⁻⁶ Although this review will focus exclusively on the role of other STDs in facilitating sexual HIV transmission, this relation must be viewed in the context of simultaneous HIV induced alterations in the natural history, diagnosis, or response to therapy of other STDs, and the bidirectional interactions between these effects.

Recent scientific evidence supporting a role for STDs in facilitating HIV transmission has come from three types of studies. Firstly, several studies have examined the biological plausibility of this association, and suggested potential mechanisms at the biological level. Secondly, cohort studies of HIV seroconversion have estimated the increase in risk of HIV infection associated with specific STDs or STD syndromes. Finally, community level intervention studies have begun to quantify the effect that STD treatment can have on HIV incidence. We will discuss each of these lines of evidence in turn.

Articles were selected from a review of Medline, accessed with the OVID search engine. Initial search criteria included all articles on ("sexually transmitted diseases" OR "syphilis" OR "simplexvirus" OR "herpes genitalis" OR "herpesvirus 2, human" OR "sexually transmitted diseases, viral" OR "chancroid" OR "gonorrhoea" OR "neisseria gonorrhoeae" OR "fallopian tube diseases" OR "adnexitis" OR "chlamydia infections" OR "trichomonas" or "trichomonas infections" or "trichomonas vaginalis" OR "trichomonas vaginitis" OR "papillomavirus, human" OR "condyloma acuminata") AND ("HIV" OR "HIV infections" OR "acquired immunodeficiency syndrome"). The OVID search of Medline covered articles from January 1987 to September 1998, and yielded 2101 articles. In addition, a variety of methods was used to uncover articles which might have been missed, including searching for related articles by

author, and combing literature reviews. In addition, all abstracts under the category "sexually transmitted diseases" from the XI and XII International Conferences on AIDS (Vancouver 1996 and Geneva 1998) and other relevant scientific meetings were reviewed. Efforts were made to locate journal articles which resulted from the research reported in the abstracts we identified. All original journal articles and abstracts which met one of the following three criteria were included in the review: (1) studies of the biological plausibility or mechanism of facilitation of HIV infectiousness or susceptibility by STDs, (2) prospective cohort studies (longitudinal or nested case-control) which estimate the risk of HIV infection associated with specific STDs or STD syndromes, or (3) intervention studies which quantitate the effect which STD treatment can have on HIV incidence. The remaining studies were excluded. These were primarily those that did not directly address relations between HIV and other STDs, and those that employed case-control or cross sectional study designs.

BIOLOGICAL PLAUSIBILITY

Promotion of HIV transmission by STDs, both ulcerative and non-ulcerative, may occur by a variety of biological mechanisms, which are likely to affect *both* HIV infectiousness and susceptibility. Firstly, other STDs facilitate HIV shedding in the genital tract, which probably promotes HIV infectiousness. This has been demonstrated by testing genital secretions for the presence of HIV and, more recently, for the HIV concentration. Secondly, STDs also appear to increase susceptibility to HIV, by recruiting HIV susceptible inflammatory cells to the genital tract and by disrupting mucosal barriers to infection. We will discuss each of these effects separately.

The relation between STDs and genital HIV shedding is potentially confounded by the level of immunosuppression, since advancing immunosuppression may promote STD acquisition or persistence,⁵ as well as HIV shedding.⁷ Evidence that the role of STDs is independent of level of immunosuppression comes from studies that adjust for level of immunosuppression in the analysis or demonstrate reduced HIV shedding after STD treatment. Therefore, these considerations are important in assessing the quality and generalisability of the results of this group of studies.

Effect of genital ulcers on HIV infectiousness and susceptibility

Genital ulcers bleed frequently during sexual intercourse, resulting in potential increases in HIV infectiousness (table 1). In HIV infected individuals, HIV has been detected frequently in genital ulcer exudates.⁸⁻⁹ Among 609 HIV-1 positive female sex workers in Cote d'Ivoire, detection of HIV-1 by cervicovaginal lavage was also markedly increased among women with cervicovaginal ulcers compared with those without lesions (55.8% versus 21.5%). This effect persisted after adjustment for level of immunosuppression (adjusted odds ratio

Table 1 Ulcerative STDs and HIV shedding

| Author, year | Study population | Ascertainment of HIV shedding | Ascertainment of other STD | Results | Comments/study limitations |
|--|---|---|---|---|--|
| Female: | | | | | |
| Ghys <i>et al</i> , 1997 ¹⁰ | 609 HIV-1 positive FSWs in Abidjan. | PCR on cervicovaginal lavage (qualitative). | GUD by clinical exam; <i>H ducreyi</i> and HSV culture; RPR/TPHA. | HIV shedding in 55.8% (29/52) FSW with GUD <i>v</i> 21.5% (120/557) without (adj OR 3.9, CI 2.1–7.4). At 1 week, HIV-1 detection more frequent if ulcers persisted | HIV-1 shedding significantly associated with immunosuppression, which was included in multivariate analysis. |
| Kreiss <i>et al</i> , 1989 ⁸ | 56 HIV positive FSWs with GUD in Nairobi. | Culture of ulcer exudate (qualitative). | GUD by exam; <i>H ducreyi</i> culture, HSV and syphilis serologies. | HIV cultured from 11% (4/36) ulcers (other cultures not evaluable owing to contamination). | |
| Male: | | | | | |
| Dyer 1998 ¹¹ | 86 HIV-1 positive men with urethritis at Malawi STD clinic (24 with GUD). | PCR (NASBA) on seminal plasma (quantitative). | GUD by exam; urethritis, see Cohen <i>et al</i> in Table 2. | Median HIV concentration in semen ($\times 10^4$ copies/ml): 21.9, 11.0, 19.5, and 0.4 for urethritis (all causes) plus GUD, urethritis alone, NGU plus GUD, and NGU alone, respectively ($p = 0.04$ for NGU plus/minus GUD). | In multiple linear regression model with GC and blood plasma HIV-1 concentration, GUD not independent predictor of seminal plasma HIV-1 concentration. |
| Plummer <i>et al</i> , 1990 ⁹ | 7 male HIV positive STD clinic patients with chancroid in Nairobi. | Culture and PCR on ulcer exudate (qualitative). | <i>H ducreyi</i> culture. | HIV cultured from 30% (2/7) ulcer swabs; 86% (6/7) ulcer swabs positive for HIV by PCR. | |
| Schacker <i>et al</i> , 1997 ¹² | 12 HIV positive men with genital herpes in Seattle. | PCR on ulcer exudate (quantitative). | HSV culture. | HIV detected in 96% (25/26) HSV-2 episodes. HSV by culture correlated with detection of HIV RNA (OR 4.6, CI 1.8–8.7). | HIV quasi-species in ulcers later appeared in serum, suggesting replication competence. |

FSW=female sex workers; GUD=genital ulcer disease; PCR=polymerase chain reaction; NGU=non-gonococcal urethritis; GC=gonorrhoea; OR=odds ratio; CI=confidence interval.

(OR), 3.9, 95% confidence interval (CI) 2.1–7.4). Among the limited number of women with ulcers who returned after approximately 1 week, successful treatment reduced HIV-1 detection to levels similar to those among women who did not have ulcers at enrolment.¹⁰ Among 86 HIV-1 infected men presenting to a Malawi STD clinic with urethritis, the presence of genital ulcer disease (GUD) increased HIV concentration in seminal plasma, particularly among those with non-gonococcal urethritis (NGU) (median copy number $\times 10^4$ 19.5 *v* 0.4 for NGU plus GUD *v* NGU alone).¹¹ However, in contrast with the findings in Cote d'Ivoire, GUD was not an independent predictor of seminal HIV shedding, but instead appeared to increase viral load in semen by increasing blood plasma HIV concentrations, possibly because GUD patients had more advanced HIV disease or systemic immune activation.¹¹ In another recent study, detection of replication competent HIV from herpetic genital ulcers was common, and was correlated with recovery of HSV-2 by culture from the lesions.¹² These findings are consistent with recent evidence that HIV transcription and plasma viral load may increase during acute episodes of HSV-1 infections.¹³

Conversely, among HIV seronegative individuals, genital ulcers may increase susceptibility to HIV by disrupting mucosal integrity, and by increasing the presence and activation of HIV susceptible cells in the genital tract.^{14–15} *Haemophilus ducreyi*, for example, evokes a cell mediated immune response which attracts HIV susceptible cells to the ulcer surface.¹⁶ In fact, *H ducreyi* may contain specific T cell stimulating antigens,¹⁷ which may further predispose T cells to infection by HIV. In addition, with viral STDs such as herpes, there may be interactions between viruses in the genital tract which promote the establishment of HIV infection. For example, in tissues co-infected with HSV-1,

HIV-1 virions appear able to infect keratinocytes that lack CD4 receptors and, therefore, are not usually vulnerable to HIV infection.¹⁸ In gaining access to cells, HIV may also take advantage of changes in cellular chemokine receptors that result from infection with other viruses, as shown recently in studies of cytomegalovirus.¹⁹

Effect of non-ulcerative STDs on HIV infectiousness and susceptibility

Non-ulcerative STDs such as gonorrhoea and chlamydia also increase HIV shedding in the genital tract (table 2), probably by recruiting HIV infected inflammatory cells as part of the normal host response. Among HIV positive men in Nairobi, prevalence of detectable HIV in genital secretions increased in the presence of gonorrhoea (adjusted OR 3.2, 95% CI 1.6–6.4) and, with successful therapy, was halved from 44% to 21%, a level similar to the 19% found among men without urethritis at enrolment.²⁰ In a US study, seminal leucocytosis also predicted HIV detection in semen (adjusted OR 7.0, 95% CI 1.3–39.3).²¹ In addition, several studies in men have documented an association between non-ulcerative STDs and increased concentration of HIV shedding by showing that HIV nucleic acid copy number in semen is elevated in the presence of non-ulcerative STDs.^{22–24} In the largest of these studies, involving 135 HIV-1 positive men in Malawi, median HIV-1 concentrations in seminal plasma were eight and 10 times higher among men with urethritis and gonorrhoea, respectively, than among men without urethritis.²³ Two weeks after appropriate treatment, HIV-1 concentrations among urethritis patients were reduced by two thirds to levels that were not significantly different from those among controls without urethritis ($p=0.9$).

Among women, data linking non-ulcerative STDs and HIV shedding are more preliminary, but growing rapidly. Investigators in Mombasa,

Table 2 Non-ulcerative STDs and HIV shedding

| Author, year | Study population | Ascertainment of HIV shedding | Ascertainment of other STD | Results | Comments/study limitations |
|---|--|--|--|--|---|
| Female: | | | | | |
| Clemetson <i>et al</i> , 1993 ²⁶ | 97 female HIV positive STD clinic patients in Nairobi. | PCR on endocervical and vaginal swabs (qualitative). | Cervical mucopus on exam; cervical GS and GC culture; vaginal wet mount and GS. | HIV shedding associated with mucopus (MPC in 22% of 27 HIV shedders <i>v</i> 7% of 56 non-shedders; adj OR 6.2, CI 0.9–41.4); association with 6 GC cases NS (unadj OR 4.3, CI 0.7–25.3). | Multivariate model included age, OCP use, pregnancy, cervical ectopy, and mucopus (not immunosuppression). |
| Ghys <i>et al</i> , 1997 ¹⁰ | 609 HIV-1 positive FSWs in Abidjan. | PCR on cervico-vaginal lavage (qualitative). | Cervical mucopus on exam; CT EIA, GC culture, vaginal wet mount. | HIV shedding associated with GC and CT (HIV detected in 34.5% of 194 with GC <i>v</i> 19.9% of 403 without, adj OR 1.9, CI 1.2–3.0; 48.2% of 27 with CT <i>v</i> 23.5% of 563 without, adj OR 2.5, CI 1.1–5.8). HIV-1 shedding reduced if STD cured. | HIV-1 shedding significantly associated with immunosuppression, which was included in multivariate analysis. |
| Kreiss <i>et al</i> , 1994 ²⁷ | 92 HIV positive FSWs in Nairobi. | PCR on endocervical swabs (qualitative). | Cervical mucopus on exam; cervical GS and Pap; CT and GC culture. | HIV shedding associated with cervicitis by GS or Pap (adj OR 8.7, CI 2.0–37.2), but not with cervical mucopus, GC, or CT. | Multivariate model included OCP use, cervicitis, pregnancy, cervical maturation value (not immunosuppression). |
| John <i>et al</i> , 1997 ²⁸ | 223 HIV-1 positive pregnant women in Nairobi. | PCR on cervical and vaginal swabs (qualitative). | Cervical mucopus on exam; GC culture, CT antigen detection, vaginal KOH prep and GS, <i>T vaginalis</i> PCR. | HIV shedding associated with mucopus (MPC in 44% of 63 HIV shedders <i>v</i> 28% of non-shedders, OR 2.1, CI 1.1–3.9). GC (OR 2.2, CI 0.7–6.4) and CT (OR 1.2, CI 0.4–3.4) associations NS. | HIV detection associated with low CD4 count, but no multivariate analysis provided to adjust for immunosuppression. |
| Mostad <i>et al</i> , 1997 ²⁵ | 318 female HIV-1 positive STD clinic patients in Mombasa, Kenya. | PCR on endocervical and vaginal swabs (qualitative). | Vaginal and cervical GS, GC and <i>T vaginalis</i> culture, CT EIA, RPR/TPHA. | HIV shedding associated with GC, and cervicitis and vaginitis by GS, but not CT or trich (HIV detected in 75% with GC <i>v</i> 49% without, <i>p</i> =0.02). | No multivariate analysis of STD, cervicitis, or vaginitis data presented. |
| Male: | | | | | |
| Anderson <i>et al</i> , 1992 ²¹ | 95 HIV positive men in Boston and San Francisco. | Semen culture (qualitative). | Seminal leucocyte counts. | HIV detection associated with seminal leucocytosis (adj OR 7.0, CI 1.3–39.3). | Multivariate model included CD4<200, symptomatic HIV disease, zidovudine therapy, and seminal leucocytosis. |
| Atkins <i>et al</i> , 1996 ²² | 4 HIV positive men with urethritis (3 with GC and 1 with NGU) in London. | PCR on semen (quantitative). | Urethral Gram stain, GC culture. | STD treatment reduced average HIV proviral DNA load from approx 450–150 copies per ml of semen (<i>p</i> <0.05). | HIV proviral loads estimated from graph; exact values not provided in article. |
| Cohen <i>et al</i> , 1997 ²³ | 135 male HIV-1 positive dermatology and STD clinic patients in Malawi. | PCR (NASBA) on seminal plasma (quantitative). | Urethral Gram stain, GC, and <i>T vaginalis</i> culture, CT LCR. | Median HIV concentration in semen ($\times 10^4$ copies/ml): 15.8, 12.4 and 1.5 in men with GC, urethritis (all causes), and no urethritis, respectively; 2 weeks after STD treatment, 4.1 (<i>p</i> =0.0001). | Men with and without urethritis had similar CD4 and blood plasma HIV RNA levels. |
| Eron <i>et al</i> , 1996 ²⁴ | 1 HIV-1 positive man with chlamydia in Chapel Hill, NC. | PCR (NASBA) on seminal plasma (quantitative). | CT culture. | CT treatment reduced HIV RNA in semen from 1 200 000 to 12 000 copies per ml (a 100-fold reduction). | Case report. |
| Moss <i>et al</i> , 1995 ²⁰ | 106 male HIV positive STD clinic patients in Nairobi. | PCR on urethral exudate (qualitative). | Urethral Gram stain, GC culture. | HIV shedding associated with GC (adj OR 3.2, CI 1.6–6.4); prevalence of HIV shedding reduced to baseline (from 44% to 21%, <i>p</i> =0.02) after GC treatment. | Multivariate model included age, CD4 count <200, and GC. HIV shedding increased with immunosuppression. |

GC=gonorrhoea; NGU=non-gonococcal urethritis; GS=Gram stain; CT=*Chlamydia trachomatis*; EIA=enzyme immunoassay; RPR=rapid plasma reagin; TPHA=*Treponema pallidum* haemagglutination assay; LCR=ligase chain reaction; MPC=mucopurulent cervicitis; OCP=oral contraceptive pills.

Kenya found that HIV shedding was associated with gonorrhoea (univariate OR 3.1 (95% CI 1.1–9.8), and Gram stain evidence of cervicitis or vaginitis, but not with chlamydia or trichomonal infection.²⁵ In the Cote d'Ivoire study mentioned above, after adjustment for level of immunosuppression in multivariate analysis, HIV was at least twice as frequently detected among women with gonorrhoea or chlamydia as among women without these STDs. The results of successful treatment of the 83 women with gonorrhoea in this study were reminiscent of the findings among men in Nairobi co-infected with HIV and gonorrhoea: the prevalence of HIV shedding fell from 42% to 24% (*p*<0.01). HIV shedding also decreased from 50% to 38% among the 16 women successfully treated for chlamydia, but the decrease did not achieve statistical significance.¹⁰

Although two studies of Nairobi prostitutes showed no statistically significant associations

between specific STDs and HIV shedding, these studies did suggest a strong correlation between HIV detection and cervical mucopus (adjusted OR 6.2, 95% CI 0.9–41.4)²⁶ or cervical inflammation by Gram stain or Pap-nicolaou smear (adjusted OR 8.7, 95% CI 2.0–37.2).²⁷ The authors speculate that extremely frequent gonococcal infection and treatment with antibiotics among their subjects may have hampered their ability to detect true associations.²⁷

Among pregnant women, genital HIV shedding has an additional dimension, the potential for increased transmission from mother to child during delivery. Pregnancy itself appears to promote HIV shedding.^{26 27} In a recent study of pregnant women, HIV detection in genital secretions was also associated with cervical mucopus, but not with gonococcal or chlamydial cervicitis.²⁸

In HIV negative individuals, non-ulcerative STDs appear to increase susceptibility to HIV

Table 3 Prospective studies of genital ulcer disease (GUD) (mixed or unspecified aetiology) and HIV seroconversion

| Author, year (design) | Study population (number of HIV seroconverters) | Ascertainment of GUD (number of cases) | Risk estimates (95% CI) | Comments/study limitations |
|---|---|--|--|--|
| Female to male transmission: | | | | |
| Cameron <i>et al</i> , 1989 ³³ (cohort) | 293 men with STDs acquired from FSWs in Nairobi, Kenya (24 SC). | <i>H ducreyi</i> culture, dark field, syphilis serology (149 cases). | Adj RR: 4.7 (1.3–17.0). | Adjusted for sexual behaviour, but limited behavioral data included. |
| Mbizvo <i>et al</i> , 1996 ^{33A} (cohort) | 1607 male factory workers in Harare, Zimbabwe (51 SC). | Self reported genital ulcer (39 cases). | Adj Cox hazard ratio 3.6 (1.5–8.3). | Adjusted for sexual behaviour, but no objective STD diagnosis. |
| Nelson <i>et al</i> , 1997 ³⁵ (nested case control) | 169 male Thai military conscripts (45 SC; 124 controls). | <i>H ducreyi</i> , HSV-2, and syphilis serology (73, 98, and 5 cases, respectively). | Adj OR 2.2 (0.9–5.5) for <i>H ducreyi</i> seropositivity; NS for syphilis (see table 4 for HSV-2). | Few syphilis cases; careful attention to adjustment for sexual behaviour. |
| Nopkesorn <i>et al</i> , 1998 ³⁴ (cohort) | 1036 male Thai military conscripts (14 SC). | Self reported GUD during and 3 years before study (210.5 and 308.4 person years, respectively); <i>H ducreyi</i> , HSV-2, and syphilis serologies. | Adj RR 13.5 (3.4–89.9) for incident GUD; unadj RR 5.4 (1.6–20.3) for GUD in 3 years before study; NS for <i>H ducreyi</i> seropositivity at enrolment. | Low HIV incidence; potential bias due to 54% loss to follow up; serological analyses limited by focus on specimens obtained at enrolment; adjusted for FSW contact and receptive anal intercourse. |
| Telzak <i>et al</i> , 1993 ³⁶ (cohort) | 758 heterosexual male STD clinic patients in NYC without history of IDU (14 SC). | RPR/MHATP, <i>H ducreyi</i> culture, Tzank smear (344 cases). | Adj OR 3.3 (1.1–10.1) for chancroid; NS for syphilis and HSV (compares GUD patients with those with non GUD STDs). | Potential selection bias due to response rate and recruitment strategy; potential misclassification bias due to lack of HSV culture or serology and frequent clinical diagnosis of chancroid. |
| Male to female transmission: | | | | |
| Plummer <i>et al</i> , 1991 ³⁷ (cohort) | 124 FSWs in Nairobi, Kenya (83 SC). | Clinical exam, <i>H ducreyi</i> culture, syphilis serology (71 cases). | Adj OR 3.3 (1.2–10.1). | Dose-response relation between GUD and HIV seroconversion; potential bias due to 37% loss to follow up. |
| Both routes of transmission: | | | | |
| DeVincenzi <i>et al</i> , 1994 ³⁸ (cohort) | 256 HIV serodiscordant couples in Europe (12 SC). | Self reported GUD (5 cases). | Unadj incidence ratio 5.2 (4.4–6.0). | No clinical or lab confirmation of STD diagnosis; no adjustment for sexual behaviour. |
| Kassler <i>et al</i> , 1994 ³⁹ (nested case control) | 147 STD clinic patients tested twice for HIV in Baltimore (49 SC; 98 matched controls). | Clinical exam, RPR from chart review (7 cases). | Adj OR 11.3 (1.6–80.2). | Retrospective cohort from convenience sample of patients tested twice for HIV; limited data on sexual behaviour. |
| Mehendale <i>et al</i> , 1995 ⁴⁰ (cohort) | 851 STD clinic patients in Pune, India (62 SC). | Clinical exam (55% of cohort diagnosed with GUD). | Adj RR 4.3 (2.2–8.4) for GUD at visit before seroconversion; 8.2 (3.8–17.9) for recurrent GUD. | Potential bias due to 26% response rate. |

SC=seroconverters; RPR=rapid plasma reagin; MHATP=microhaemagglutination assay for antibodies to *Treponema pallidum*; RR=risk ratio; NS=not significant; OR=odds ratio.

by recruiting HIV target cells to the endocervix. For example, the median concentration of endocervical CD4 lymphocytes was almost twice as high among 32 HIV negative STD clinic patients with gonorrhoea, chlamydia, or trichomoniasis as among 32 patients without these infections (476 v 245 per 10 000 cells, $p<0.001$).²⁹ In addition, in vitro data suggest that *Chlamydia trachomatis* not only recruits polymorphonuclear leucocytes, but may also interact with these cells to increase HIV replication.³⁰

SEROCONVERSION STUDIES

Recent prospective studies of new HIV infections in the presence of STDs have made the leap from biological plausibility to observed phenomenon. In the majority of these studies, to document the temporal sequence of STD acquisition and HIV seroconversion, groups of initially HIV negative people were followed with repeated physical examinations and HIV tests, although some studies relied on self reports of STDs. Importantly, a number of these studies included enough seroconversions to control for sexual behaviour as a potential confounder of the relation between STDs and HIV infection. We will discuss only prospective studies, and will emphasise those that used objective STD detection methods and adjusted for sexual behaviour. For summaries of case-control and cross sectional studies, we refer the reader to several recent reviews.^{5 31 32}

Genital ulcer disease of mixed or unspecified aetiology and HIV transmission

Nine prospective studies address genital ulcer disease (GUD) of mixed or unspecified aetiology (table 3). In this group of studies, the authors presented measures of risk of HIV seroconversion associated with genital ulcers, regardless of aetiology. Overall, six of these nine studies used an objective STD detection method to document active infection (that is, clinical or laboratory examination) and adjusted for sexual behaviour. All six showed a strong effect of GUD on HIV acquisition, with adjusted odds ratios or risk ratios between 2.2 and 11.3.

Five of these studies address female to male HIV transmission. Cameron and colleagues³³ studied 293 men who had acquired an STD from female sex workers in Nairobi, Kenya. The ulcers they acquired were primarily (89%) chancroid. Overall, 24 men seroconverted to HIV, and those with ulcers were almost five times as likely to acquire HIV as those without GUD, even after adjustment for sexual behaviour. A second study, conducted among factory workers in Zimbabwe, also reported a more than threefold increase in risk of HIV seroconversion among those with self reported genital ulcers, despite the study's limitation of failing to use clinical or laboratory methods to detect GUD.^{33A} Two studies conducted in Thailand examined cohorts of male conscripts during their 2 years of military service. One of these, a cohort study of 1036 men of whom 14 became

Table 4 Prospective studies of genital herpes (HSV) and HIV seroconversion

| Author, year (design) | Study population (number of HIV seroconverters) | Ascertainment of HSV (number of cases) | Risk estimates (95% CI) | Comments/study limitations |
|--|---|---|--|---|
| Female to male transmission: | | | | |
| Nelson <i>et al</i> , 1998 ³⁵ (nested case control) | 169 male Thai military conscripts (45 SC; 124 controls). | HSV-2 antibody (98 cases). | Adj OR 3.1 (1.2–7.9). | Randomly selected controls; careful attention to adjustment for sexual behaviour. |
| Nopkesorn <i>et al</i> , 1998 ³⁴ (cohort) | 1036 male Thai military conscripts (14 SC). | HSV-2 antibody (166 cases). | Unadj RR 4.1 (1.1–13.5) Adj. RR NS. | Adj RR 2.0 (0.6–6.1) for seropositivity at enrolment; no data provided on seroincident HSV-2 infection during study; potential bias due to 54% loss to follow up. |
| Telzak <i>et al</i> , 1993 ³⁶ (cohort) | 758 male heterosexual STD clinic patients in NYC without history of IDU (14 SC). | Clinical exam, Tzanck smear (95 cases). | Unadj RR 1.1 (p>0.20) (compares herpes patients with those with non-GUD STDs). | Potential selection bias due to response rate and recruitment strategy; potential misclassification bias due to lack of HSV culture or serology. |
| Male to male transmission: | | | | |
| Holmberg <i>et al</i> , 1988 ⁴¹ (nested case control) | 104 homosexual men in San Francisco tested \geq twice for HIV (47 SC; 57 matched controls). | HSV-2 antibody (58 cases, including 15 HSV-2 SC). | HSV-2 seropositivity in 68% HIV SC <i>v</i> 46% controls, p<0.02; HSV-2 SC in 42% HIV SC <i>v</i> 14% controls, p<0.02. | Associations significant after log linear analysis of sexual behaviour (p=0.02); by our calculation, unadj ORs 2.5 (1.1–6.2) and 4.4 (1.1–18.1), respectively. |
| Keet <i>et al</i> , 1990 ⁴² (nested case control) | 107 homosexual men in Amsterdam (53 SC; 54 matched controls). | HSV-2 antibody (53 cases, including 6 HSV-2 SC). | HSV-2 seropositivity in 71% HIV SC <i>v</i> 38% controls, p<0.05 (unadj OR 4.0 (1.7–9.8) our calculation); HSV-2 SC unadj OR 2.2 (0.4–12.1). | Authors conclude HSV-2 not a risk factor despite results; number of sex partners similar for cases/controls, no other control for sexual behaviour; small numbers HSV-2 SC. |
| Kingsley <i>et al</i> , 1990 ⁴³ (nested case control) | 98 homosexual men in Pittsburgh (49 SC; 49 matched controls). | HSV-2 antibody (42 cases, including 7 HSV-2 SC). | HSV-2 seropositivity matched OR 1.0 (0.3–2.9). | Cases and controls matched on number of receptive anal intercourse partners; no other adjustment for sexual behaviour. |
| Kuiken <i>et al</i> , 1990 ⁴⁴ (nested case control) | 235 homosexual men in Amsterdam (84 SC; 151 matched controls). | Self reported anogenital herpes (29 cases). | Unadj OR 6.0 (2.34–13.7). | OR significant after control for sexual behaviour in log linear analysis. |
| Craig <i>et al</i> , 1995 ⁴⁵ (nested case control) | 375 homosexual men in Vancouver (125 SC; 250 controls). | Self reported herpes (76 cases). | Unadj OR 1.3 (0.8–2.2). | Controls randomly selected; no attempt to distinguish between primary and recurrent genital HSV. |

SC=seroconverters; IDU=injecting drug use; OR=odds ratio; RR=risk ratio.

HIV infected, found that men who self reported GUD during the study were more than 13 times as likely to HIV seroconvert as those who did not report acquiring a genital ulcer.³⁴ Although *H ducreyi*, HSV-2 and syphilis serologies were obtained at enrolment, these markers of earlier infection were not associated with increased risk of incident HIV infection. The second study used a nested case-control design with careful adjustment for sexual behaviour and documented a two to threefold increased risk of HIV seroconversion among men with serological evidence of *H ducreyi* or HSV-2 during the study period.³⁵ Finally, in New York City, Telzak and colleagues³⁶ studied 758 heterosexual men attending an STD clinic, of whom 14 HIV seroconverted. Chancroid was not as common in this study as in that by Cameron *et al*, but still accounted for 40% of GUD cases. People with chancroid were about three times as likely to HIV seroconvert as those who were not infected. Significant associations were not detected for syphilis or herpes, but misclassification bias may have occurred because almost 40% of chancroid cases were diagnosed on clinical criteria, and HSV cultures were not obtained.

Male to female transmission of HIV was studied among 124 female sex workers in Nairobi. After adjustment for sexual behaviour, those who developed GUD were three times as likely to HIV seroconvert as those who remained free of STDs (adjusted OR 3.3, 95% CI 1.2–10.1).³⁷

Three articles examined HIV seroconversion for men and women in the same analysis. In a study of 256 serodiscordant European couples, HIV seroincidence was five times as high among non-index partners with self reported genital ulcers as among those without STDs.³⁸

This result was statistically significant, although cases of GUD were too few to control for sexual behaviour. In a Baltimore STD clinic, among a retrospectively defined cohort of 147 clinic returnees tested at least twice for HIV, after adjustment for sexual behaviour, those with GUD were 11 times more likely to seroconvert than those without infection.³⁹ Finally, among members of a large cohort of patients at two STD clinics in Pune, India, patients who had GUD on examination at their pre-seroconversion visit were more than four times as likely to seroconvert as those who did not. Furthermore, those who had GUD both before and after HIV seroconversion were more than eight times as likely to acquire HIV infection. It could not be determined whether the GUD present in the second visit (after seroconversion) was acquired at the same time as HIV, or at some other time, before or after seroconversion.⁴⁰

Genital herpes and HIV transmission

Eight studies specifically address genital herpes as a factor in HIV seroconversion (table 4). Prospective data linking genital herpes with increased risk of HIV transmission are more equivocal than those for genital ulcers, particularly of bacterial aetiologies. This may be due, in part, to the fact that HSV-2 infection is a chronic disease manifested by recurrent anogenital ulcers, the frequency and severity of which decline in most patients over time. Therefore, while studies that use HSV-2 serology offer the advantage of a sensitive and specific ascertainment of HSV infection status, this measure may correlate poorly with recent genital ulceration which is the risk factor of importance. This means that studies of seroprevalent herpes, especially those in which

serologies are obtained only at enrolment, may underestimate the impact of herpetic ulcers on HIV transmission. Despite these considerations and the fact that some of the studies are limited either by use of insensitive HSV detection methods or by failure to adjust for sexual behaviour, in aggregate, they suggest that genital herpes, particularly new infection resulting in HSV-2 seroconversion, may be associated with HIV acquisition.

Three studies address heterosexual transmission, in this case, female to male. In the two studies mentioned above that were conducted among Thai military conscripts, HSV-2 infection was detected serologically. After adjustment for sexual behaviour, in the nested case-control study, HSV-2 antibodies were three times as common among HIV seroconverters at the study visit before that at which HIV seroconversion was documented as among persistently HIV negative men at the analogous visit (adjusted OR 3.1, 95% CI 1.2–7.9).³⁵ However, in the cohort study in which HSV-2 antibodies were obtained only at enrolment, the fourfold increase in risk of HIV seroconversion that was observed in bivariate analysis fell to a twofold relative risk that failed to achieve statistical significance after adjustment for sexual behaviour (adjusted risk ratio (RR) 2.0, 95% CI 0.6–6.1).³⁴ In the third study, there was no association of genital herpes with HIV acquisition, but ascertainment of HSV infection (by clinical examination and Tzanck preparation) was probably so insensitive that many HSV infections were missed.³⁶

Three additional analyses which employed the more sensitive measure, HSV-2 antibody, were all conducted in homosexual men. Holmberg *et al*⁴¹ studied HSV-2 antibody among 47 HIV seroconverting homosexual men and 57 matched controls in San Francisco, USA, and found that HSV-2 seropositive men were significantly more likely to acquire HIV than those without HSV-2 antibody. HSV-2 seroconversion resulted in an even greater increase in risk of HIV seroconversion. These associations persisted after potential confounding by sexual behaviour was addressed through log linear analysis. A similar nested case-control study of homosexual men in Amsterdam also documented increased risk of HIV acquisition associated with HSV-2 seropositivity.⁴² Only one of the three analyses, a nested case-control study of homosexual men in San Francisco matched on prior level of receptive anal intercourse,⁴³ failed to show an association between genital herpes and increased risk of HIV acquisition. Interestingly, of the two other studies which were conducted among homosexual men and relied exclusively upon self reported herpes as the outcome measure, one⁴⁴ found a strong association, and the other⁴⁵ was unable to document any relation.

Syphilis and HIV transmission

Nine studies examined the role of syphilis in HIV acquisition (table 5). The majority are limited either by small numbers of syphilis cases or by reliance on self reported history to

ascertain a syphilis diagnosis. However, four of the six studies with 10 or more syphilis cases revealed a significant association between syphilis and increased risk of HIV transmission on multivariate analysis, with risk estimates that range from 2.3 to 8.6.^{44 46–48} The other two studies, one conducted using clinical and laboratory indicators of syphilis among heterosexual men in New York³⁶ and the other conducted using self reported syphilis among homosexual men in Vancouver,⁴⁵ reported univariate risk estimates of 3.4 and 3.8, respectively, but these associations did not remain significant after adjustment for sexual behaviour.

Of the six studies with sufficient numbers of syphilis cases to permit multivariate analysis, two were conducted among heterosexuals,^{36 46} three among homosexual men,^{44 45 47} and one did not restrict the analysis with respect to route of sexual transmission.⁴⁸ In Miami, investigators found that among a retrospective cohort of 106 women who were HIV negative during antenatal testing on average 3.8 years earlier, those who became HIV infected were more than eight times as likely to have serological evidence of syphilis documented in their medical records since their pregnancies than women who remained free of HIV infection (adjusted OR 8.6, 95% CI 1.0–84).⁴⁶ In contrast, the New York study of heterosexual male STD clinic patients mentioned above did not demonstrate a significant association between syphilis and HIV acquisition on multivariate analysis.³⁶ This may have reflected, in part, the fact that syphilis patients were compared with non-GUD STD clinic patients rather than with men who did not receive an STD diagnosis. All three studies that were conducted among homosexual men relied on self reported history of syphilis, which is neither sensitive nor specific for detection of the disease. Nevertheless, two of these studies reported unadjusted odds ratios of 2.3 and 3.5 which remained significant in multivariate analysis.^{44 47}

Strong evidence that syphilis facilitates HIV transmission is also provided by the remaining study of over 5100 patients who were tested twice for HIV at four Miami STD clinics.⁴⁸ Patients who were diagnosed with syphilis between the two HIV tests were almost three times as likely to HIV seroconvert as those who were diagnosed with syphilis before the first HIV test. These patients, in turn, were almost one and a half times as likely to seroconvert as those in whom syphilis was never diagnosed. The first of these analyses included only patients who had had syphilis at some point, and who shared behavioural risk factors for syphilis. Assuming that these risk factors remained stable over time, the ratio of HIV incidences in the two groups represents a measure of the additional risk of acquiring HIV incurred by having syphilis during an HIV exposure. Uniquely, this study also adjusted for the higher prevalence in Miami of HIV infection among syphilis patients than among patients with other STDs. This factor contributes importantly to the true population attrib-

Table 5 Prospective studies of syphilis and HIV seroconversion

| Author, year (design) | Study population (number of HIV seroconverters) | Ascertainment of syphilis (number of cases) | Risk estimates(95% CI) | Comments/study limitations |
|---|--|--|---|---|
| Female to male transmission: | | | | |
| Nelson <i>et al</i> , 1998 ³⁵ (nested case control) | 169 male Thai military conscripts (45 SC; 124 controls). | VDRL/TPHA (5 cases). | Unadj OR 1.5 (0.02–27.6). | Low numbers of syphilis cases. |
| Nopkesorn <i>et al</i> , 1998 ³⁴ (cohort) | 1036 male Thai military conscripts (14 SC). | RPR/MHATP (34 prevalent plus 7 incident cases). | Unadj RR 2.0 (0.1–14.3) for seropositivity at enrolment. | Too few incident syphilis cases to permit analysis; potential bias due to 54% loss to follow up. |
| Telzak <i>et al</i> , 1993 ³⁶ (cohort) | 758 male heterosexual STD clinic patients in NYC without history of IDU (14 SC). | Clinical exam, RPR/MHATP, dark field, history of exposure (123 cases). | Unadj RR 3.4 (p=0.09); Adj OR not significant. | Potential selection bias due to response rate and recruitment strategy; compares patients with syphilis with those with non-GUD STDs. |
| Male to female transmission: | | | | |
| Dominguez <i>et al</i> , 1996 ⁴⁶ (nested case control in retrospective cohort) | 106 women in Miami from random sample of 407 testing HIV negative on average 3.8 years earlier during antenatal care (10 SC; 96 controls). | Syphilis serology from medical records (11 cases). | Adj OR 8.6 (1.0–84). | Adjusted for condom use, number of lifetime sex partners, and sex partner at risk for HIV. |
| Laga <i>et al</i> , 1993 ⁵¹ (nested case control) | 431 FSWs in Kinshasa, Zaire (68 SC; 126 matched controls). | RPR/TPHA (9 cases). | Unadj OR 3.4 (0.7–17.6). | Few syphilis cases; syphilis not included in multivariate analyses. |
| Male to male transmission: | | | | |
| Craib <i>et al</i> , 1995 ⁴⁵ (nested case control) | 375 homosexual men in Vancouver (125 SC; 250 controls). | Self reported syphilis (14 cases). | Unadj OR 3.8 (1.3–10.8). | Controls randomly selected; OR not significant in multivariate model. |
| Darrow <i>et al</i> , 1987 ⁴⁷ (cohort) | 359 homosexual men in San Francisco (240 SC). | Self reported treatment for syphilis (101 cases). | Unadj OR 3.5 (1.9–6.2). | OR significant after control for sexual behaviour in multivariate analysis. |
| Kuiken <i>et al</i> , 1990 ⁴⁴ (nested case control) | 235 homosexual men in Amsterdam (84 SC; 151 matched controls). | Self reported syphilis (98 cases). | Unadj OR 2.3 (1.3–4.1). | OR significant after control for sexual behaviour in log linear analysis. |
| All routes of transmission: | | | | |
| Otten <i>et al</i> , 1994 ⁴⁸ (retrospective cohort) | 5164 STD clinic patients in Miami (208 SC). | Syphilis serology from medical records (1913 P&S or latent cases). | “Quasi-adjusted” incidence ratio 2.9 (1.9–4.3)—for those diagnosed with syphilis between HIV tests compared with that of those diagnosed before first HIV test. | Incidence ratio for syphilis diagnosis before first HIV test <i>v</i> no syphilis diagnosis 1.4 (1.0–1.9). |

SC=seroconverters; IDU=injecting drug use; VDRL=Venereal Diseases Research Laboratory; TPHA=*Treponema pallidum* haemagglutination assay; RPR=rapid plasma reagin; MHATP=microhaemagglutination assay for antibodies to *Treponema pallidum*; P&S=primary and secondary syphilis; OR=odds ratio; RR=risk ratio; GUD=genital ulcer disease.

utable risk of syphilis, but it may upwardly bias the estimate of the facilitating effect of syphilis on HIV transmission.

Non-ulcerative STDs and HIV transmission

Non-ulcerative STDs also appear to play a role in facilitating HIV transmission, with risk estimates from 13 prospective studies that are largely similar to those for ulcerative STDs (table 6). However, the relative importance of ulcerative and non-ulcerative STDs in HIV transmission is probably complex. If the effect of non-ulcerative STDs on HIV acquisition is, indeed, in the range indicated by these studies, the ultimate impact of non-ulcerative STDs on the HIV epidemic could potentially be much greater than that of GUD because non-ulcerative STDs are far more common than genital ulcers in most populations. On the other hand, the impact of non-ulcerative STDs may be more limited than that of GUD for two reasons. Firstly, HIV infection does not alter the natural history or response to therapy of non-ulcerative STDs to the same extent that it does for GUD.⁵ Thus, the “epidemiological synergy” that fuels the mutually reinforcing spiral of infection observed with ulcerative STDs and HIV infection is far more modest or absent with non-ulcerative STDs. Secondly, the available data suggest (tables 3–6) and it is biologically plausible that, while genital ulcers increase HIV risk bidirectionally for both

receptive and insertive sex partners (for example, among heterosexuals for both female to male and male to female transmission), non-ulcerative STDs may increase risk primarily for the receptive partner. Almost all of the studies specifically supporting a role for gonorrhoea, chlamydial infection, or trichomoniasis document an increased risk of *male to female* HIV transmission (table 6). The two exceptions are a study of STD clinic patients in which the increased HIV risk was carried by those individuals who experienced male to female HIV transmission,³⁹ and a study of homosexual men in which rectal gonorrhoea, but not urethral or pharyngeal infection, was associated with HIV acquisition in multivariate analysis.⁴⁵ Mathematical models may be helpful in understanding the dynamic interplay of these factors in a range of settings.

Gonorrhoea and HIV transmission

Eleven of the 13 prospective studies of non-ulcerative STDs specifically address gonococcal infection. Of these, nine showed a statistically significant association of gonorrhoea with HIV seroconversion, although in two of the studies^{47 49} the association did not remain significant in multivariate analysis and in one⁵⁰ no attempt was made to adjust for sexual behaviour (table 6). Risk estimates in the six remaining studies^{39 45 51–53} ranged from 3.2 to

Table 6 Prospective studies of non-ulcerative STDs and HIV seroconversion

| Author, year (design) | Study population (number of HIV seroconverters) | Ascertainment of non-ulcerative STDs (number of cases) | Risk estimates (95% CI) | Comments/study limitations |
|---|--|--|--|---|
| Female to male transmission: | | | | |
| Nopkesorn <i>et al</i> , 1998 ³⁴ (cohort) | 1036 male Thai military conscripts (14 SC). | Self reported urethritis during study (224.7 person years). | Adj RR for incident urethritis 6.0 (1.8–20.9). | Adjusted for FSW contact and receptive anal intercourse, but no objective STD diagnosis; potential bias due to 54% loss to follow up. |
| Male to female transmission: | | | | |
| Dominguez <i>et al</i> , 1996 ⁴⁶ (nested case control in retrospective cohort) | 106 women in Miami from random sample of 407 testing HIV negative on average 3.8 years earlier during antenatal care (10 SC; 96 controls). | From medical records, GC culture (8 cases); CT EIA (16 cases); trich wet mount (11 cases). | Adj ORs: GC 23.5 (2.3–383) CT 10.7 (1.8–84) Trich 4.7 (0.5–41.1). | Adjusted for condom use, number of lifetime sex partners, and sex partner at risk for HIV; unadj OR for trich 3.7 (1.1–12). |
| Kapiga <i>et al</i> , 1998 ⁵² (cohort) | 2471 women at 3 FP clinics in Dar es Salaam, Tanzania (75 SC). | GC culture (42 cases); trich wet mount (164 cases). | Adj RR: GC 3.8 (1.7–8.5); trich NS. | STD tests obtained at baseline only; potential bias due to 45% loss to follow up. |
| Kilmarx <i>et al</i> , 1997 ⁴⁹ (cohort) | 285 FSWs in Chiang Rai, Thailand (30 SC). | CT and GC nucleic acid hybridisation; trich wet mount (number of cases NA). | Adj RRs: CT 3.4 (1.4–7.8); GC and trich NS. | “Dose response:” CT unadj RR 3.6 (1.4–9.7) w/1 pos test, 10.4 (4.3–25.2) w/≥2 pos tests; GC unadj RR 3.5 (1.4–9.0) and 6.2 (2.0–19.3), respectively. Trich unadj RR 2.0 (0.3–14.7). |
| Laga <i>et al</i> , 1993 ⁵¹ (nested case control) | 431 FSWs in Kinshasa, Zaire (68 SC; 126 matched controls). | GC culture (59 cases); CT EIA (30 cases); trich wet mount (52 cases). | Adj ORs: GC 4.8 (2.4–9.8); CT 3.6 (1.4–9.1); trich 1.9 (0.9–4.1). | See also Laga <i>et al</i> , 1994 ⁵⁸ for related analysis. |
| Plourde <i>et al</i> , 1994 ⁵⁰ (cohort) | 81 female STD clinic patients, with GUD in Nairobi, Kenya (10 SC). | GC culture (7 cases); PID by clinical exam (5 cases). | Unadj RRs: GC 5.0 (1.0–19.2); PID 6.3 (1.9–20.4). | Potential bias due to 40% loss to follow up and lower STD rates in 81 subjects than in 53 LTFU; small numbers of HIV and STD cases; no adjustment for sexual behaviour. |
| Plummer <i>et al</i> , 1991 ³⁷ (cohort) | 124 FSWs in Nairobi, Kenya (83 SC). | CT and GC culture (CT 38 cases; GC mean 0.2 (SD 0.3) cases/month). | Adj ORs: CT 2.7 (0.9–7.8); GC NS. | Potential bias due to 37% loss to follow up; GC relatively rare among subjects. |
| Taha <i>et al</i> , 1998 ⁵³ | 1196 pregnant women in Blantyre, Malawi (27 SC). | GC culture (34 cases); trich wet mount (275 cases); BV by clinical criteria (274 cases) | Adj ORs: GC 4.3 (1.2–15.7); BV 3.7 (p=0.04, test for trend with increasing severity); trich NS. | Estimated attributable risk of BV 23%. |
| Weir <i>et al</i> , 1994 ⁵⁴ (nested case control) | 273 FSWs in Yaounde, Cameroon (17 SC; 68 controls). | GC culture (32 cases). | Unadj OR: GC 2.2 (0.7–6.6); adj OR 1.4 (0.4–4.9). | For adj OR, condom/N 9 use from coital logs as continuous variable, data reliability unclear. |
| Male to male transmission: | | | | |
| Craib <i>et al</i> , 1995 ⁴⁵ (nested case control) | 375 homosexual men in Vancouver (125 SC; 250 controls). | Self reported GC (27 urethral, 7 pharyngeal, and 16 rectal cases). | GC unadj ORs: urethral 2.8 (1.3–5.8), pharyngeal 5.2 (1.2–23.0), rectal 4.7 (1.8–12.8); rectal GC adj OR 3.2 (p=0.04). | Urethral and pharyngeal GC NS on multivariate analysis. |
| Darrow <i>et al</i> , 1987 ⁴⁷ (cohort) | 359 homosexual men in San Francisco (240 SC). | Self reported treatment for GC (266 cases). | Unadj OR: GC 3.0 (1.9–4.9). | OR not significant in multivariate analysis; no subanalysis of rectal GC. |
| All routes of transmission: | | | | |
| Kassler <i>et al</i> , 1994 ³⁹ (nested case control) | 147 STD clinic patients tested twice for HIV in Baltimore (49 SC; 98 matched controls). | Chart review for GC, GS, and culture (31 cases), trich by wet mount (9 cases). | Adj OR: GC 5.1 (1.3–19.3); trich unadj OR 2.5 (0.7–9.3). | Trich assessed only in women, small number of cases detected, NS on multivariate analysis. |
| Mehendale <i>et al</i> , 1995 ⁴⁰ (cohort) | 851 STD clinic patients in Pune, India (62 SC). | Urethritis/cervicitis on exam ± GS (171 urethritis and 35 cervicitis cases). | Adj OR 3.0 (1.4–6.5) for urethritis/cervicitis before seroconversion; 3.7 (1.1–13.2) for recurrent infection. | Potential bias due to 26% response rate; no laboratory confirmation of aetiology. |

SC=seroconverters; GUD=genital ulcer disease; FSW=female sex workers; FP=family planning; CT=*Chlamydia trachomatis*; EIA=enzyme immunoassay; GC=gonorrhoea; BV=bacterial vaginosis; PID=pelvic inflammatory disease; GS=Gram stain; RR=risk ratio; OR=odds ratio; NS=not significant.

5.1 with the exception of one study which reported an adjusted odds ratio of 23.5.⁴⁶

The majority of the studies of gonorrhoea examine male to female HIV transmission. Three relatively large studies of family planning clinic clients in Dar es Salaam, antenatal clinic patients in Blantyre, and female sex workers in Kinshasa,^{51–53} documented adjusted risk estimates of 4.2, 4.3, and 4.8, respectively, while a smaller study of women identified through prenatal care in Florida found an adjusted odds ratio of 23.5 with a wide confidence interval.⁴⁶ Another smaller study of female STD clinic patients in Nairobi found an unadjusted relative risk of 5.0.⁵⁰ However, three additional studies of male to female gonorrhoea transmission among female sex workers in Chiang Rai, Cameroon, and Nairobi

failed to show a significant association with HIV acquisition in multivariate analysis.^{37 49 54}

The smaller sample sizes with more limited numbers of HIV seroconversions or relatively low incidences of gonorrhoea in two of these studies^{37 54} may, in part, explain these divergent results.

One study addresses gonorrhoea and HIV transmission among both men and women. In this study, conducted among STD clinic attenders in Baltimore,³⁹ gonorrhoea was associated with a fivefold increase in risk of HIV seroconversion. As mentioned above, unpublished subgroup analyses suggested that the increased risk here, too, was carried primarily among those individuals experiencing male to female transmission (unadjusted OR 7.2 (CI 0.8–64) for male to female transmission, and

Table 7 Population attributable risk of STDs for HIV seroconversion

| | Genital ulcers | Syphilis | Gonorrhoea | Chlamydia | Trichomoniasis |
|--|----------------|----------|------------|-----------|----------------|
| Male clients CSWs in Nairobi, Kenya (Cameron <i>et al</i> , 1989 ³³) | 69% | | | | |
| CSWs in Nairobi, Kenya (Plummer <i>et al</i> , 1991 ³⁷) | 44% | | | 25% | |
| CSWs in Kinshasa (Laga <i>et al</i> , 1993 ⁵¹) | | | 44%* | 22%* | 18%* |
| STD clinic attenders in India (Mehendale <i>et al</i> , 1995 ⁴⁰) | 54% | | | | |
| STD clinic patients in Baltimore, MD, USA (Kassler <i>et al</i> , 1994 ³⁹) | 7% | | 26% | | |
| STD clinic patients in Miami, FL, USA (Otten <i>et al</i> , 1994 ⁴⁸) | | 18%* | | | |

Included in this table were studies which presented an odds ratio for the given STD which was adjusted for behaviour, and which supplied sufficient information for the calculation of population attributable risk (PAR).

PAR was calculated from the adjusted odds ratio and the proportion of cases (seroconverters) who had the exposure (STD) of interest. (PAR=(1 - 1/adj OR) (prevalence of STD among HIV seroconverters)).⁴⁴

*Indicates that the PAR was presented in the article itself, and agreed with our calculations; all other figures are from our calculations.

2.0 (CI, 0.8–4.9) for female to male transmission (William Kassler, personal communication)).

Unfortunately, there are few prospective data on male to male transmission of gonorrhoea. The two published studies conducted among homosexual men both relied upon self reports of gonorrhoea and found that gonococcal infection was associated with HIV seroconversion in univariate analysis.^{45 47} On multivariate analysis, one study found that rectal gonorrhoea increased risk of HIV acquisition three-fold, while urethral and pharyngeal infection were no longer associated with increased risk.⁴⁵ The other study, which did not include analyses by anatomical site of gonococcal infection, no longer revealed a significant association.⁴⁷

Other non-ulcerative STDs and HIV transmission

Other non-ulcerative STDs such as chlamydial infection and trichomoniasis are also linked to HIV seroconversion, although fewer studies have addressed these diseases, perhaps because accurate detection of these organisms is more technically difficult than is detection of gonorrhoea (table 6). In the two studies from Africa in which chlamydia was diagnosed in women by enzyme immunoassay (EIA)⁵¹ and by culture,³⁷ adjusted odds ratios were 3.6 and 2.7, respectively. A third study conducted among women in Miami using EIA reported and adjusted odds ratio of 10.7 with wide confidence intervals.⁴⁶ Trichomonal infection in women was found to be associated with HIV acquisition (with borderline statistical significance) in Kinshasa,⁵¹ but not in Blantyre or Baltimore.^{39 53} One group at a Nairobi STD clinic found that clinically diagnosed pelvic inflammatory disease (PID) was strongly associated with HIV acquisition, with unadjusted odds ratio of 6.3.⁵⁰ Although PID itself would be unlikely to increase HIV transmission risk, it may be assumed that PID in this study is a proxy for previous infection with gonorrhoea, chlamydia, or other pathogens. Finally, two prospective studies considered the role of urethritis or cervicitis in HIV transmission. In a study of both men and women at an STD clinic in India, Mehendale and colleagues found an association between HIV acquisition and urethritis or cervicitis, with an adjusted odds ratio of 3.0 (95% CI 1.4–6.5).⁴⁰ Self reported urethritis was also strongly associated with HIV acquisition among male Thai military conscripts (adjusted RR 6.0, 95% CI 1.8–20.9).³⁴ Recent evidence suggests that bacterial vaginosis,

which is not an STD, but which causes abnormal vaginal discharge, may also increase risk of HIV infection, although the biological mechanism responsible for this finding is not yet clear.^{52 55}

POPULATION ATTRIBUTABLE RISK OF STDs FOR HIV TRANSMISSION AND MATHEMATICAL MODELS

A number of the HIV seroconversion studies discussed above provide sufficient information to calculate, for a given study, the population attributable risk (PAR) of various sexually transmitted diseases for HIV acquisition (table 7). The PAR is a measure of the proportion of cases of disease in a population that could, theoretically, be averted by removing a given exposure if an intervention were able to achieve complete coverage and optimal effectiveness. It takes into account not only the magnitude of the risk associated with the exposure, but also the prevalence of the exposure in the population of interest.⁵⁶ Vittinghoff and Padian⁵⁷ discuss the strengths and limitations of the PAR as applied to STDs. It should be noted that in the specific case of studies of HIV seroconversion related to other STDs, the PAR may substantially underestimate potentially avertable cases because it reflects only the effect of STDs on HIV susceptibility and does not capture the effect on HIV infectiousness.

PARs for GUD were generally higher than those for non-ulcerative STDs. It is interesting to note that the PARs of GUD in studies conducted in the developing world were higher (44%–69%) than in those conducted in the United States (7%–18%), largely reflecting the lower prevalence of these diseases in the United States than in developing countries. This observation underscores the fact that a given PAR applies specifically to the population studied at a given phase of an epidemic, and may not easily translate to other populations. In the United States, for example, the STD attributable HIV transmission risk could feasibly be increasing, as heterosexual modes of transmission assume a larger role in HIV epidemiology.

Mathematical models of the impact of other STDs on HIV transmission suggest that the effect of these diseases may be much greater than is suggested by studies using standard epidemiological analytical approaches to estimate effects at a given time. Dynamic models may more accurately reflect the explosive way in which the effect of STDs is multiplied through ongoing HIV transmission.^{58–61} Some models suggest that STD incidence and preva-

lence may be critical to sustaining heterosexual transmission of HIV infection. Modelling also suggests that the effectiveness and cost effectiveness of STD treatment in HIV prevention may be greater during earlier stages of an HIV epidemic, before HIV infection becomes widely distributed^{62–65} and the relative importance of incurable viral STDs, like herpes, begins to increase. Finally, mathematical models highlight the importance of providing STD treatment to those who are most likely to transmit infection to others in order to maximise the population level impact and cost effectiveness of STD control interventions.⁶⁶

INTERVENTION TRIALS

Although very valuable, the observational studies discussed above are inherently subject to a number of potential limitations, and they cannot directly measure the effect of STD control on HIV incidence in the larger population.^{5 58 67–70} Quasi-experimental intervention projects conducted among female sex workers (FSWs) in Zaire, Kenya, and Bolivia have shown that routine STD clinical services and condom promotion may be associated with dramatic reductions in HIV incidence or prevention of epidemic increases in HIV infection in high risk populations.^{71–73} In the Zairian study, for example, HIV incidence rose from 2.7 per 100 women years among FSWs who attended more than 90% of their monthly clinic visits to 7.1, 20.3, and 44.1 per 100 women years among FSWs who attended 76–90%, 50–75%, and less than 50% of their scheduled visits, respectively.⁷¹ However, without randomised, controlled designs, these studies, too, have limited ability to demonstrate causal relations and estimate the magnitude of the intervention effect.

Two community level randomised, controlled intervention trials have been conducted in Africa, the first in the Mwanza region of Tanzania, and the second in the Rakai district of Uganda. Both of these trials attempted to quantitate the effect of STD treatment on HIV incidence by randomising entire communities to receive either some form of augmented STD treatment or the local standard of STD care. A third community level randomised, controlled trial is currently ongoing in the Masaka district of Uganda. Its three arms compare the effect on HIV incidence of (i) behavioural intervention to promote safer sex, and (ii) improved STD management plus the behavioural intervention, with a comparison group receiving community development activities.

Mwanza trial: improved clinic based treatment of symptomatic STDs to reduce HIV incidence

Investigators in Mwanza, Tanzania, provided continuous access to improved treatment for symptomatic STDs through existing primary healthcare clinics in six rural communities.⁷⁴ The intervention included training of staff from health centres and dispensaries in STD diagnosis and treatment using syndromic algorithms, assuring a regular supply of drugs, implementing routine supervisory visits to health facilities, and establishing an STD

reference clinic and laboratory. In addition, health educators in the intervention areas visited villages to provide information on STDs, focusing on the availability of effective treatment and encouraging prompt treatment of symptomatic STDs. For 24 months the six matched, comparison communities received STD clinical services that were unchanged from those that had existed previously, at which time the intervention was also implemented in the comparison communities.

After 24 months, this intervention resulted in a 38% reduction in HIV incidence in the intervention communities compared with the control communities.⁷⁴ In each of the six communities that received this relatively modest intervention, HIV incidence was substantially lower than in the corresponding matched comparison community (range 12%–65%). Importantly, the greatest impact of the intervention was in women aged 15–24 years, and men aged 25–34, groups in which the HIV incidence was highest in the comparison communities. Significant reductions were documented in the prevalence of serologically diagnosed syphilis (RPR $\geq 1:8$; adjusted RR 0.71, 95% CI 0.54–0.93) and borderline significant reductions were observed in the prevalence of new cases of syphilis (RPR $\geq 1:8$; adjusted RR 0.62, 95% CI 0.38–1.02) and of symptomatic urethritis in the previous year (adjusted RR 0.51, 95% CI 0.25–1.03).⁷⁵ These results were not associated with changes in sexual behaviour or condom use that might confound the association between improved STD treatment and HIV transmission.

Economic analysis of the STD treatment intervention in Mwanza showed that it was cost effective in preventing HIV infection at US\$218 per HIV infection averted and \$10 per disability adjusted life year (DALY) saved.⁷⁶ These estimates compare favourably with other effective and widely implemented public health interventions such as childhood immunisation (estimated cost effectiveness \$12–17 per DALY saved).⁷⁶

Rakai trial: intermittent home based mass treatment of STDs to reduce HIV incidence

In Rakai, Uganda, investigators tested another approach to STD treatment for HIV prevention.⁷⁷ In the intervention communities, which were grouped into five clusters of four to seven villages reflecting social and sexual networks, directly observed mass treatment for curable STDs was provided irrespective of symptom status at 10 month intervals in subjects' homes using single dose antibiotics (oral azithromycin, ciprofloxacin, and metronidazole and intramuscular benzathine penicillin for serological evidence of syphilis). In the five control community clusters, home based mass treatment was provided in a single blinded fashion using an antihelminth (mebendazole), iron folate, and low dose multivitamins. Symptomatic subjects who were encountered in control communities during mass treatment rounds were referred for STD care to the project's mobile clinics which were available only during these periods. All study subjects

were offered HIV prevention education and serological counselling, condoms, and free general health care at the project's mobile clinics.

After three mass treatment rounds that spanned 20 months and included two follow up intervals, HIV incidence was similar in the intervention and control communities overall (adjusted rate ratio 0.97, 95% CI 0.81–1.16) and in each of the randomised pairs.⁷⁷ By the third round, significant reductions were observed in the prevalence of serologically diagnosed syphilis (adjusted prevalence ratio 0.80, 95% CI 0.71–0.89) and trichomoniasis (adjusted prevalence ratio 0.59, 95% CI 0.38–0.91), and in the incidence of trichomoniasis (adjusted RR 0.52, 95% CI 0.35–0.79), but not of syphilis. Borderline significant reductions in bacterial vaginosis (BV) prevalence also occurred (adjusted prevalence ratio 0.87, 95% CI 0.74–1.02).

Mwanza and Rakai results: consistent or contradictory?

Why did STD treatment dramatically reduce HIV incidence in Mwanza, but not in Rakai? Although superficially the results of these two landmark, community level, randomised, controlled trials may appear contradictory, in fact, the two studies tested different STD treatment interventions using different measurement approaches in populations with different HIV and STD epidemiology. The findings are, not surprisingly, different, but consistent and complementary.

Among the multiple factors that may have contributed to the divergent results of the two trials at least four explanations probably combined to produce the dramatic reduction in HIV incidence in Mwanza and the equally stunning absence of effect on HIV incidence in Rakai.

Firstly, in light of the frequency with which most individuals have sex, it is logical that continuous access to improved STD treatment services would be more effective than intermittent mass treatment administered as infrequently as every 10 months. For example, in Rakai, individuals who became infected within days after a mass treatment round had few STD treatment options for the next 10 months other than the inadequate clinic care that had existed before the trial.

Secondly, symptomatic STDs may be more important than asymptomatic infections in facilitating HIV transmission, while asymptomatic STDs may be more central to ongoing spread of STDs and development of sequelae. Biologically, this is because symptomatic STDs are more likely than asymptomatic cases to be associated with fulminant inflammatory responses or larger ulcers, factors that facilitate HIV transmission. Asymptomatic STDs, on the other hand, are more likely to persist untreated and, as a result, spread to others or progress to complications in the original patient. Symptomatic STDs also often reflect recently acquired or incident infections and, therefore, recent risky sexual behaviours. Thus,

focusing on symptomatic STDs may be a very effective way to target STD treatment interventions.

Thirdly, as discussed above, STDs may play a greater role in HIV transmission in earlier than in later phases of an HIV epidemic. As HIV epidemics mature and infection becomes widely disseminated in the population, exposure of the limited number of individuals who remain biologically and behaviourally susceptible becomes increasingly independent of cofactors such as STDs. Furthermore, the relative contribution of curable STDs may decline in late HIV epidemics as viral STDs like genital herpes become common. The Rakai district was experiencing a far more advanced HIV epidemic during that study than the Mwanza region was during its trial, with baseline HIV prevalence of 16% and 4%, respectively.^{74 77}

Finally, local STD incidence, prevalence, and aetiological spectrum are critical determinants of the impact of any STD treatment intervention on HIV transmission. The STD detection methods used in the Rakai study were much more sophisticated and extensive than those used in the Mwanza trial, making direct comparisons difficult. However, the available data suggest that while syphilis prevalence rates were probably comparable in the two study populations, gonorrhoea and chlamydia prevalence may have been slightly higher in Mwanza and the proportion of genital ulcers due to HSV-2 was probably substantially higher in Rakai.

Implications for policy and practice

The extensive observational and growing intervention trial data leave little doubt that other STDs facilitate HIV transmission through direct, biological mechanisms.^{78 79} The question is no longer *whether* STD detection and treatment should be an essential component of HIV prevention programmes, but rather *how* this component should be implemented to have maximal impact on HIV incidence in specific populations.⁸⁰

The intervention studies currently suggest that intermittent mass treatment, alone, delivered to the general population is not an effective approach to STD control for HIV prevention, particularly in a late HIV epidemic with relatively low rates of curable STDs. However, targeted mass treatment (for example, among high frequency transmitters or others with high STD incidence or prevalence) at relatively short intervals deserves additional examination in combination with establishment of high quality, continuous STD treatment services to achieve a rapid, initial reduction in STD rates as a "lead in" to more comprehensive, sustained STD control measures.

Policy makers, HIV prevention programme managers, and providers must focus initial implementation efforts on three key areas: (i) improving access to and quality of STD clinical services; (ii) promoting early and effective STD related healthcare behaviours; and (iii) establishing surveillance systems to monitor STD and HIV trends and their interrelation. Guide-

lines addressing these areas have recently been published in the United States,⁸⁰ and UNAIDS and the World Health Organisation are planning to develop analogous guidelines to assist developing country programmes.

Initial steps to ensure access to and quality of STD clinical services should, at a minimum, focus on *public* and *private* settings that serve individuals who are HIV infected or at high risk for HIV acquisition. These steps should include assessing and ensuring timely access to quality STD diagnostic and treatment services for symptomatic people seeking care; establishing or expanding STD screening in medical and non-medical settings for asymptomatic people who are at high risk for HIV infection and other STDs; and providing relevant training to programme managers and clinicians.⁸⁰ In industrialised countries, STD screening strategies in venues such as substance abuse treatment centres, correctional institutions, HIV counselling and testing sites, schools, and community centres in high morbidity areas may capitalise on the advent of urine based nucleic acid amplification tests and single dose antibiotic regimens. In developing countries, where resource constraints frequently preclude widespread use of aetiological tests, primary emphasis should be placed on assuring access to high quality STD clinical services for symptomatic people in medical and non-medical settings. This will require widespread training of providers in the use of algorithms for syndromic STD management, which perform well in the diagnosis of genital ulcers and urethritis.⁸¹ It will also necessitate re-evaluation of vaginal discharge algorithms which have limited sensitivity and specificity in detection of cervicitis,⁸¹ as well as a greater commitment to assure consistent availability of effective STD drugs at local levels. Providing HIV counselling, testing, and referral to individuals diagnosed with other STDs is clearly an important complementary strategy.

Promotion of early and effective STD related healthcare behaviours must begin to complement the important risk reduction messages that, in many parts of the world, currently focus almost exclusively on sexual behaviours. The critical new messages for individuals at risk for HIV infection and other STDs include (i) other STDs facilitate the spread of HIV infection, thus STD detection and treatment is an HIV prevention strategy; (ii) recognising and acting on STD symptoms are important; and, in settings where screening is feasible, (iii) most STDs occur without symptoms, so regular screening is vital. People must also be provided with specific information about sources of STD services. A complementary set of messages must be developed for providers.⁸¹

An essential condition for effective and cost effective implementation of STD treatment as an HIV prevention strategy is establishment at the local level of basic STD and HIV surveillance systems with linkages that permit policy makers, programme managers, and providers to determine, in their community, the extent of overlap between STD and HIV infected populations and, therefore, the relative

importance locally of STD treatment in the mix of HIV prevention strategies. These systems should also provide information on the aetiological spectrum of STDs. These data must be analysed, disseminated, and used on a routine, timely basis to guide decision making as both HIV and STD epidemics evolve.

In summary, STD control is a central priority in its own right. Almost two decades into the most devastating pandemic of our times, we have strong evidence that early detection and treatment of other STDs can be a powerful addition to the HIV prevention arsenal in populations with substantial burdens of curable STDs, particularly in early HIV epidemics. While we must continue to refine our understanding of how best to implement STD control to prevent HIV transmission in specific populations, initial steps to assess potential impact and, where epidemiologically appropriate, incorporate STD treatment as part of a comprehensive HIV prevention strategy are clear. We must not hesitate any longer to take those steps.

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From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection.

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