The facilitation of HIV transmission by other sexually transmitted infections during sex between men

Evidence regarding epidemiological synergy among gay men in the UK

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Briefing Paper

Preface

Sigma Research's CHAPS R&D *Briefing Papers* aim to provide a focussed research briefing in a particular area of interest to people engaged in HIV/AIDS health promotion.

In March 1998, a national HIV health promotion collaborative planning group (including Sigma Research) published *Making It Count,* a collaborative planning framework for reducing the incidence of HIV infection through sex between men (CHAPS SDG, 1998). Making It Count proposed that HIV prevention target other sexually transmitted infections (STIs) among homosexually active men in order to reduce the overall probability of HIV transmission during those HIV exposures that occur. This R&D Briefing Paper looks in closer detail at the potential of STIs as targets for reducing HIV incidence, in order to inform future strategic planning of HIV health promotion.

Sigma Research endeavours to facilitate HIV health promotion through the dissemination of research findings in clear, accurate and credible documents. Towards this end, we are assisted by many individuals who are willing to read earlier, wordier and usually more tortuous drafts of papers such as these. This briefing on HIV and STIs has benefited from the attention of: Clare Johnson (Bristol Royal Infirmary Milne Centre GUM Department); Neil Macdonald and Barry Evans (Public Health Laboratory Services AIDS & STD Centre); Andy Chaffer (SLAP-fM, Birmingham); Richard Scholey, Shaun Whelan, Will Nutland, Jack Summerside and Colin Dixon (Terrence Higgins Trust, London); Chris Woolls (Gay Men's Health Matters, Brighton); Tom Doyle (Yorkshire MESMAC, Leeds) and David Reid and Laurie Henderson (at Sigma Research). We would like to express our thanks to all of these readers and commentators.

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April 1999

Published on behalf of the CHAPS Partnership

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ISBN: 1 872956 55 6

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First published April 1999
Reprinted June 2000

1 Introduction

It is likely that far more exposures to HIV infection occur during sex between men than do HIV transmissions. That is, far more HIV uninfected men engage in unprotected anal intercourse with HIV infected men, than become infected doing so. A key question for HIV prevention is 'What distinguishes those HIV exposures which result in transmission from those which do not?'. One of the potential answers to this question is 'the presence of another sexually transmitted infection in either the HIV infected or HIV uninfected partner'.

STIs (sexually transmitted infections) and HIV are widely perceived to have a complex and multi-faceted inter-relationship. This relationship is sometimes described as 'synergistic' because it is believed that HIV and (at least some) STIs each facilitate the transmission of the other. A reduction in the prevalence of STIs has not traditionally been a strategic target for reducing HIV incidence, although a number of calls for greater integration of HIV and STI prevention programmes have been made. Reasons to consider this integration are outlined below.

Epidemiological synergy

The question of whether to prioritise STI prevention on the basis of their contribution to the probability of HIV transmission depends on *how much* impact it is thought this would have on HIV incidence. If STIs make no contribution to transmission, or if they did but were never present when HIV exposure occurred, then targeting them on this basis would be unjustified. If the contribution is considerable and STIs are at least occasionally present, or the contribution is small but STIs are often present, then targeting STIs to reduce HIV incidence can be considered, irrespective of the approaches used to influence the targets.

Affinity of approaches

There are likely to be considerable benefits in integrating HIV and STI prevention work. This may be the case irrespective of any epidemiological synergy. That is, even if STIs play no part in the HIV epidemic, attempts to prevent, diagnose, treat or manage STIs and HIV may be mutually reinforcing.

Condom use for anal intercourse reduces the probability of transmission of HIV and most other STIs. In addition, the concepts and basic knowledge used in HIV education can be easily utilised in STI education, and vice versa. This may increase return visits to clinics, and assist in decisions about how 'regular' the inevitably recommended clinic visit should be. Building on men's knowledge of HIV as a virus, like hepatitis, will also help men understand the possibility of an HIV vaccine.

Further, increasing knowledge of and access to hepatitis vaccinations will usually increase overall access to GUM services, including HIV testing, possibly prior to symptomatic infection with an STI. A positive experience in such circumstances may lead to increased access to advice or counselling, HIV testing and other clinical services. Also, although HIV may be the first STI a gay man gets, if it is not, acquisition of a genital or anal STI can raise awareness of the possible consequences of unprotected anal intercourse.

Integrating programmes where the approaches adopted for HIV prevention differ from the approaches adopted for STI prevention is more problematic. For example, the routine screening applied to many STIs would usually be considered unacceptable for HIV.

Organisational efficiency

Of course, with finite resources with which to reduce HIV incidence, in the absence of epidemiological synergy, an HIV prevention programme cannot simply extend its remit to STI prevention without detracting from its impact on HIV incidence. If HIV prevention programmes are to be expanded to encompass STI prevention, then appropriate reallocation of resources are necessary.

HIV prevention programmes and STI prevention programmes are both likely to be more cost-effective if integrated. This is especially the case with relatively small populations with high levels of HIV and STI infection. STIs are responsible for considerable morbidity among gay men in the UK, and gay men account for a disproportionate amount of STI-related morbidity in the UK population. As the prevention, diagnosis and treatment of STIs are themselves goals of the Health Service, the extension of programmes concerned with HIV infection through sex between men to cover other STIs could have considerable health benefits for relatively little additional cost.

1.1 SCOPE OF THE PAPER

The first aim of the paper is to give HIV health promoters a basic knowledge of sexually transmitted infections, to facilitate engagement with all three reasons to consider HIV and STI programme integration: epidemiological synergy, affinity of approaches and organisational efficiency. Since epidemiological synergy is the least accessible of the three debates, this paper also aims to make available evidence of the likely synergy among gay men in the UK, such that strategic decisions can be informed by the available research. Hence, this paper outlines the possible relationships between sexually transmitted infections and the probability of HIV transmission when exposure occurs. The two key questions addressed are:

a are people without HIV infection, who are exposed to HIV, more susceptible to infection if they are infected with some other STI at the time?

b are people with HIV infection, when their infection is exposed to others, more likely to transmit HIV if they are also infected with other STIs at the time?

If either or both of these relationships are significant contributory factors to HIV incidence among gay men in the UK, the following questions will also be pertinent:

c Does having HIV infection increase people's susceptibility to some STIs?

d Are the manifestations of STIs more serious and persistent if people also have HIV infection?

e Are people with HIV infection more likely to develop AIDS if they are repeatedly infected with other STIs?

Irrespective of the answers to **a** and **b**, HIV health promotion concerned with maintaining or improving the health of people with HIV infection (ie. AIDS prevention rather than HIV prevention) has a stake in the answers to **c**, **d** and **e**. While all three of these later questions need to be answered to fully understand any synergistic relationship between STIs and the HIV epidemic in the UK, they are substantially beyond the scope of this paper.

2 Sexually transmitted infections: agents, diseases and symptoms

'Infection' occurs when a microbe enters the body, establishes itself and multiplies. The term sexually transmitted infections (STIs) is an umbrella term covering infection with a variety of organisms which can be passed on during sex. There are more than 25 micro-organisms which are infectious to humans and which are transmitted via sexual activity. Infectious agents (the things that are actually passed from one person to another) include viruses and bacteria, more complex multi-celled organisms and fungii. Table 2 gives some examples of these different types of agent. As crabs and scabies multiply on the surface of the body and not in it, they are not strictly infections, but infestations.

Table 2: Some different types of sexually transmitted agents and the diseases they can cause

Type of infectious agent	Specific examples of agents	Disease they can cause
Viruses (bundled strands of genetic material)	Hepatitis A	Viral hepatitis
	Hepatitis B	
	Hepatitis C	
	Herpes simplex (HSV-1 & HSV-2)	Herpes
	Human immunodeficiency virus (HIV)	Acquired Immune Deficiency Syndrome (AIDS)
	Human papilloma virus (HPV)	(genital and anal) Warts
	Molluscum contagiosum	Molluscum
Bacteria (single cell organisms)	*Chlamydia trachomatis*	Chlamydia
	Haemophilus ducreyi	Chancroid
	Neisseriae gonorrhoeae (the gonococcus bacterium)	Gonorrhoea ('the clap')
	Treponema pallidum	Syphilis
	A large number of unidentified bacteria	Non-specific urethritis (NSU)
Protozoa (multi-cell organisms)	*Giardia lamblia*	Diarrhoeal illnesses
	Entamoeba histolytica	
Fungii (yeasts)	*Candida albicans*	Candidiasis ('thrush')
Arthropods (tiny animals)	*Sarcoptes scabiei* (a mite)	Scabies
	Phthirus pubis (the crab louse)	Pediculosis pubis ('crabs')

'Disease' refers to the general pathological (sick) changes brought about by an infection (or some other cause), or the specific changes brought about by a specific agent or family of agents. Because the outward manifestations of infections (diseases) were often named before the agent was known (or the disease was known to be infectious), names for diseases do not always match with what causes them. Also, some infections can give rise to more than one disease (eg. HPV also causes cervical cancer), whilst, some diseases can be caused by more than one agent (viral hepatitis distinguishes the (three) diseases caused by the hepatitis A, B and C viruses, from hepatitis caused by other things, such as alcohol or treatment drugs).

'Symptoms' are the outward signs of infection. The distinction between symptom and disease is less clear, with Latin terms for symptoms being used as names for diseases when their cause is not precisely known. Sexually transmitted infections have a diverse impact on the bodies they infect, giving rise to a range of symptoms. The most common presenting symptoms of STIs amongst gay men are outlined below (adapted from Adler, 1995; Institute of Medicine (IOM), 1996).

- urethral discharge – pus or blood being discharged from penis.
- rectal discharge – pus or blood being discharged from rectum or present in faeces.
- anal discomfort and pain.
- painful defecation or urination.
- genital ulceration – sores on head of penis or foreskin.
- anal ulceration – sores around anus.
- genital or anal warts – warts on head, foreskin or shaft of penis or around anus.

A collection of symptoms that usually occur together is known as a syndrome. There is no one-to-one relationship between an infectious agent and the syndrome of symptoms it causes. Rather, there is a matrix of agents and associated syndromes. For example, urethritis can be caused by infection with gonorrhoea, chlamydia and other organisms. We will not attempt to detail which infectious agents are associated with each symptom since medical diagnosis remains a substantial specialism outside the remit of this paper.

Equally outside our realm is treatment of infections. However, it is worth noting that: insect infestation can usually be exterminated with lotions; most bacterial and fungal STIs can be cured (with antibiotics and anti-fungals); while most viral infections cannot (although many of the diseases they cause can be managed). Hepatitis A and B are the only infections against which a vaccine exists.

The majority of viral STIs appear to be most efficiently transmitted during sex between men via the same route as HIV (ie. unprotected anal intercourse). However, some are also transmitted during other sexual acts such as oral-penile and oral-anal contact. For most viral STIs, these other routes of infection are less efficient than unprotected anal intercourse and so probably account for a relatively small proportion of transmissions (IOM, 1996).

Some infections (eg. scabies and herpes), can also be transmitted by non-sexual routes (and their appearance in an assumed monogamous partner does not necessarily mean that the relationship is not monogamous).

3 STIs commonly acquired through sex between men

All of the genito-urinary medicine (GUM) clinics in England & Wales have a statutory obligation to return quarterly data on all diagnoses of sexually transmitted infection. These returns are made via a form known as a KC60, which reports on each diagnosed condition rather than individual patients. While repeat visits with the same condition should only be reported once, any patient with multiple infections will have each reported separately. Age group and (for men) presumed sexual orientation are reported for some conditions. The Public Health Laboratory Service has responsibility for collation of KC60s and their most recent report includes data from 213 clinics across England (Simms *et al.,* 1998).

The most common STIs amongst the general population in England are, in descending order: genital warts; candida; non-specific genital infection; chlamydia; genital herpes; and gonorrhoea (Simms *et al.,* 1998). Chancroid is rare in the UK.

Among men across England, 8% of all acute STIs for which sexual orientation was recorded were homosexually acquired (Simms *et al.,* 1998). The most commonly reported STIs amongst gay men in 1996 are shown below. This data is somewhat limited because many STIs remain undiagnosed or are diagnosed in primary care settings and are therefore not reported within this system (especially infections such as scabies, pubic lice and hepatitis).

Table 3: Newly diagnosed STIs reported from genito-urinary medicine clinics in England in 1996 by male sexual orientation (adapted from Simms *et al.,* 1998)

Condition	Number of diagnoses made in men	Number presumed homosexually acquired (% of all men in brackets)
Non-specific genital infection	52,369	3,509 (6.7)
Genital warts	46,309	2,370 (5.1)
Gonorrhoea	8,939	1,996 (22.3)
HIV	2,192	1,378 (62.9)
Genital herpes	11,406	864 (7.6)
Scabies	4,257	831 (19.5)
Chlamydia	20,257	414 (2.0)
Molluscum	3,238	308 (9.5)
Other hepatitis	880	124 (14.1)
Hepatitis B	445	116 (26.1)
Syphilis	763	114 (14.9)

Some infections disproportionately affect homosexually active men. Most notable in this regard are: hepatitis B (26%), gonorrhoea (22%), scabies (20%), syphilis (15%), and 'other' hepatitis (14%).

The markedly high prevalence of hepatitis B among gay men is supported by a study of GUM clinic attenders (Gilson *et al.,* 1998). However, a study of the prevalence of hepatitis A demonstrated no difference between homosexual and heterosexual males attending a London GUM clinic (controlling for demographic factors and HIV status), despite higher rates of oral-anal sex in the former (Nandwani *et al.,* 1994).

PHLS figures suggest recent increases in diagnoses of male homosexually acquired infections. For example, between 1995 and 1996, diagnoses of uncomplicated gonorrhoea rose by 23% with rises occurring in all age groups (Simms *et al.,* 1998). There were significant increases in homosexually acquired gonorrhoea in North Thames, West Midlands, North West and Anglia & Oxford. The data gives no details about site of infections or transmission routes.

Other STIs are also increasingly common among homosexually active men (such as chlamydia and genital herpes which each rose by 18%), and these PHLS figures are supported by other studies in Leeds (Lacey *et al.,* 1997) and South London (Low *et al.,* 1997). However, not all STIs follow this pattern with some becoming less common (for example genital warts, diagnoses of which fell by 6%).

4 Looking at causes

That the agents listed in Table 2 are the causes of the diseases listed has generally been established by evidence generated by epidemiology, the study of the distribution, causes and effects of diseases in populations (not only infectious ones). When drawing conclusions about causality based on research evidence, a number of questions have to be asked about what the data tell us and what they do not. Bradford-Hill (1971) developed a number of criteria by which arguments based on data can be judged. The easiest of these to grasp is *biological plausibility.*

4.1 BIOLOGICAL PLAUSIBILITY

The criteria of biological plausibility says that we need a theory (or a number of theories) about how other STIs increase the probability of transmission of HIV. This is based in the biology of HIV transmission. Key features of whether or not infection occurs are: the size of the viral inoculum (how much virus is transferred); the viral phenotype (what particular 'brand' of the virus it is); and host susceptibility (how 'open to infection' the uninfected partner is).

The first hypothesis under consideration is that people with HIV infection, when their infection is exposed to others, are more likely to transmit HIV if they are also infected with another STI at the time, than if they are not. The theory as to why this occurs is that having another STI increases viral shedding in people with HIV, which increases the amount of virus that is transferred in semen. Although the importance of HIV shedding in transmission has not been proven, the model is supported by studies of people with HIV that have demonstrated:

- the presence of HIV in genital ulcers (Kreiss *et al.,* 1986; Plummer *et al.,* 1991);
- the increased prevalence of HIV DNA in swab specimens from men with gonorrhoea (Moss *et al.,* 1995);
- the increased concentration of cell-free HIV RNA in semen from men with gonorrhoea (Hoffman *et al.,* 1996; Atkins *et al.,* 1996);
- that CD4 receptor cells concentrate in areas with compromised membranes (Wolff & Anderson, 1988); and
- a reduction in cell-free HIV after STI treatment (Cohen *et al.,* 1997)

In addition, Cohen *et al.'s* study (1997) on HIV shedding in men with urethritis, indicates that shedding in semen can act independently of blood plasma viral levels, therefore having an impact on the infectiousness of men with HIV in latent periods of HIV infection where their infectiousness would normally be reduced.

The second hypothesis under consideration is that people without HIV infection, who are exposed to HIV, are more susceptible to infection if they are infected with some other STI at the time than if they are not. The main theory is that STIs increase the susceptibility of individuals to infection with HIV by compromising their mucous membranes and genital tract, which would usually act as a barrier to HIV (Stamm *et al.,* 1988). This notion is supported by reports that CD4 receptor cells concentrate around areas of damage (Fauci, 1993); and by studies of sero-discordant couples, in which HIV negative partners who developed STIs were subsequently more likely to become infected with HIV than were those HIV negative partners who did not have STIs (Deschamps *et al.,* 1996). Of course this may be explained by sexual practices within

the couples, that is, those whose sexual practice puts them at most risk of STIs also puts them at most risk of HIV exposure. That the theory is biologically plausible is not in question.

Before considering Bradford-Hills other criteria, we will outline the different research designs that can be used to generate evidence for the facilitative role of STIs in HIV transmission.

4.2 RESEARCH DESIGNS

The extent to which exposure to one thing (called the explanatory or independent variable) increases the risk of another (called the dependent variable) can be examined using descriptive research methods (such as cohort, case control and cross sectional studies) or quasi-experimental studies. In order to understand the following data, it is useful to consider the following ways of designing a study to examine the effects of STI exposure on the risk of HIV infection.

In *cohort studies,* a group of individuals are followed over time and their STI exposure and HIV sero-status are periodically assessed. Investigators try to establish whether those individuals who are exposed to STIs more frequently are more likely to go on to become infected with HIV. In so doing, they develop a statistical measure of risk called 'relative risk', which is the incidence of HIV amongst the STI exposed group divided by the incidence of HIV in the STI unexposed group.

In *case control studies,* a group of individuals who are already infected with HIV are compared with a group who are similar, except they are not infected with HIV. Investigators retrospectively examine differences in the exposures to STIs in individuals belonging to each group, to assess if certain STIs appear to be risk factors for HIV infection. Case control studies cannot report on relative risk since they cannot say what the incidence of HIV is in either the STI-exposed or STI-unexposed groups (because retrospective rather than prospective data is being used).

In *cross sectional surveys,* investigators examine whether there is any association between HIV status and STI history among a sample of HIV sero-positive and negative individuals. These studies differ from case control studies because there is no attempt to match members of the HIV sero-negative group with members of the HIV sero-positive group in terms of other factors such as age, sexual behaviour *etc.*

In *quasi-experimental studies,* investigators would allocate individuals to groups and follow them over time, manipulating the groups in some way and observing the differences in the groups manipulated and those not.

4.3 OTHER CRITERIA FOR JUDGING CAUSAL ARGUMENTS

Strength of association

How often does one thing cause the other? Or how much more likely is something to occur if something else is present? Here we are interested in how much more likely HIV transmission is in the presence of another STI than without one. Strength of association is usually measured by the relative risk and is expressed as so many more times more likely. In order for such ratios to be convincing they must be based on studies which measure STI exposure and HIV infection in a valid and consistent manner. Clottey & Dellabetta (1993) argues that recall failure and failure of investigators to differentiate between episodes of treated and untreated STIs are key methodological flaws in some studies. Mertens *et al.* (1990) stress the value of serological tests which can distinguish between new and old infections. Wasserheit (1992) suggests that some STIs may be more persistent in those infected with HIV than those who are not, leading to confounding.

Consistency between studies

Evidence for an association is more convincing if different studies report similar findings regarding any association.

Specificity

This refers to the need for studies to minimise the effects of confounding factors. One must be convinced that the reported difference in the dependent variable, eg. HIV infection, results only from differences in the independent variable, eg. STI exposure, and not from any other factors, such as sexual behaviour. This is why the matching of cases is so important, and explains why cross-sectional studies, where there is no matching, are particularly weak. When studies include measures of confounding factors, such as sexual behaviour, as well as of STI exposure and HIV infection this means that complex statistical operations can be performed on the data to establish whether apparent associations between STIs and HIV are in fact the result of confounding factors, or are genuine.

Even in studies which have attempted to control for such factors as age and sexual behaviour, there is likely to be some residual confounding, both because of unconsidered factors and/or because of inaccuracies in data recording. Studies attempt to control for confounders in different ways, making comparison difficult. Studies which seek to look at risk factors among gay men who know their HIV status, or who refer for HIV testing, are also more likely to be confounded by other factors, such as increased likelihood for men who have acquired STIs to test for HIV (Norton *et al.,* 1997) which may be a function of increased perception of risk (Tyndall *et al.,* 1994).

Temporality

This refers to the need to question whether the possible cause, such as STI infection, actually precedes the effect, HIV infection. This is why cohort studies and quasi-experimental studies provide stronger evidence than case control or cross sectional studies, because they enable researchers to establish which occurred first. Quinn (1996) suggests that, even in prospective studies, temporality is sometimes difficult to assess because identifying the time frame of STI infection is difficult.

Biological gradient

This refers to the need to establish that dose and effect are related. In order to judge whether there is a causal relation, we would want, for example, to see that the more STI exposure there is, the more risk of HIV infection there is.

A further criteria, not listed by Bradford-Hill, is applicability of the study population. It may be, for example, that STIs function as cofactors in HIV infection in developing, but not developed countries, or between men and women but not between men. In judging the relevance of studies for informing policy in UK gay men's HIV prevention, the applicability of international evidence to domestic circumstance needs to be considered. Furthermore, it is difficult to generalise from GUM clinic-derived samples, since these differ from the general population samples, though it is thought this is less the case with UK gay men than with other groups (Johnson *et al.,* 1994).

5 Evidence for relationships between HIV and STIs

This section summarises findings from a number of studies which have generated evidence for relationships between HIV infection and other STIs, the bulk of which present evidence for their role in increasing the susceptibility of the HIV negative partner.

5.1 ULCERATIVE STIS (HERPES, SYPHILIS) & HIV SUSCEPTIBILITY

Wasserheit (1992) concludes that the evidence for *genital ulcer disease* as a risk factor for HIV acquisition is the most compelling. Genital ulcer disease (GUD) is the generic name for those infections which commonly produce ulcerative lesions. In developed countries the cause of GUD is usually viruses from the herpes family. Out of 10 studies of GUD (all from heterosexually active samples in developing countries) six found significant relationships with HIV acquisition, controlling for sexual behaviour. In addition, one small study of gay men (Keet *et al.,* 1990) reports a small impact of GUD on HIV risk.

Some studies (Plummer *et al.,* 1991) show a relationship between the annual frequency of GUD and HIV sero-conversion, in which the average number of annual ulcer episodes was significantly higher in women who became HIV positive (sometimes called the dose effect criteria, see Wasserheit, 1992). Other studies (Boulos *et al.,* 1992) also support a dose relationship by showing a stronger relationship for the association of HSV-2 with HIV compared with syphilis and HIV. Since people with HSV-2 have more outbreaks of ulcerative lesions than do those with syphilis, this is consistent with the premise that repeated disruptions of genital mucous membranes increases the efficiency of sexual transmission of HIV, especially to women.

It is worth noting, however, that studies reported here assess the contribution of STIs to HIV infection at the level of populations. At an individual level, the probability of HIV transmission (per exposure) which STIs produce is likely to be much larger. Hayes *et al.* (1995) have estimated that genital ulcer disease may increase the per exposure risk of HIV transmission during unprotected vaginal intercourse by a factor of 10 to 50 for male to female (in vaginal intercourse) and by a factor of 50 to 300 from female to male. No such estimates have been produced for anal intercourse between men.

Studies of syphilis alone have usually found a significant relationship with HIV, at least among the heterosexually active. Prospective studies (Van Raden *et al.,* 1989; Craib *et al.,* 1995) report no significant effects, while retrospective studies report some effects. Two (Hook *et al.,* 1992; Schoenbach *et al.,* 1993) report strong significant relationships (with risk ratios over 7), though these did not control for sexual behaviour. Others (Quinn *et al.,* 1990; Elifson *et al.,* 1993) report more moderate relationships (risk ratios 3.2-3.4). The single cohort study with gay men (Van Raden, 1989) yielded a weaker result than case control studies (Elifson *et al.,* 1989; Stamm *et al.,* 1988). It is likely that the better control for behaviour and temporality in Van Raden's study, rather than STI exposure measurement, explains this difference.

Considering *herpes simplex virus* (HSV) alone, studies of heterosexually active men and women usually find a significant relationship with HIV, which persists when variations in sexual

behaviour are controlled for. One cohort study of gay men (Kuiken *et al.,* 1990) reports a strong link between HSV and HIV but it is so poorly reported it is difficult to assess the utility of the result. Of 3 prospective studies amongst gay men (Holmberg *et al.,* 1988; Kingsley *et al.,* 1990; Van Raden *et al.,* 1989), one yielded a strong correlation, where HSV seroconversion rather than HSV status was assessed (Holmberg *et al.,* 1988). This may reflect the more aggressive symptoms of primary HSV facilitating HIV infection more effectively than recurrent HSV. The other two prospective studies involving gay men did not demonstrate a significant association between HSV status and HIV. One case control study of gay men did, however, indicate a risk (Stamm *et al.,* 1988) but confounding factors were considerable.

Dickerson *et al.,* (1996) conclude that about two thirds of studies report an association between ulcerative STIs and HIV infection. They point out case control studies were more likely to show a strong association than cohort studies, but that where confounding factors were more adequately controlled for, the association was weaker. Clottey & Dallabetta (1993) also conclude that evidence of an association is most compelling regarding HIV and ulcerative STIs, which they suggest may be synergistic.

5.2 NON-ULCERATIVE STIS & HIV SUSCEPTIBILITY

Wasserheit (1992) concludes that data on the interaction of non-ulcerative STIs and HIV is more limited. However, any effect of non-ulcerative STIs will be important in the overall attributable risk of HIV at a population level in the developed world, since non-ulcerative STIs are much more prevalent amongst both gay men and other groups.

Two studies (Schoenbach *et al.,* 1993; Craib *et al.,* 1995) suggest a relatively weak relationship between gonorrhoea and HIV acquisition, though neither rule out some effect of confounding factors. Two prospective studies of gay men (Darrow *et al.,* 1987; Kingsley *et al.,* 1987) assessed STIs by self report rather than clinical or laboratory evidence, probably resulting in an under-reporting of STIs, and consequently reducing the studies ability to detect any relationship which may be present.

There is also some evidence for a relationship between ano-genital warts and HIV acquisition (Kiviat *et al.,* 1990) especially when laboratory evidence rather than self reporting is used to assess STI exposure. This data was, however, from a case control study, and so some caution is necessary in interpretation (see explanation of temporality above).

There is little evidence to suggest that hepatitis A, B or C act as co-factors for HIV transmission (but see flawed studies by Beck *et al.,* 1996, in the case of hepatitis B and Jaffe *et al.,* 1983, in the case of hepatitis non-B, that suggest the contrary).

Dickerson *et al.,* (1996) also suggest that non-ulcerative STIs are likely to be important in facilitating HIV infection in developed countries because of their greater prevalence. They suggest that non-ulcerative STIs appear to have more impact on heterosexually active women's susceptibility to HIV infection than men's, but draw no conclusions regarding homosexually active men.

5.3 COLLECTIVE IMPACT OF STIS ON HIV SUSCEPTIBILITY

For STIs taken together, three studies (Darrow *et al.,* 1987; Page-Shafer *et al.,* 1997; Williams *et al.,* 1996) report significant effects in reasonably sound prospective and retrospective studies. It appears that STIs as a whole have some impact on risk of HIV infection. The effects of ulcerative STIs amongst homosexually active men appear less dramatic than amongst heterosexually active men and women, although it is difficult to say whether this is because of different research methods. The evidence regarding non-ulcerative STIs and HIV infection is not clear but suggests an association (Schoenbach *et al.,* 1993; Craib *et al.,* 1995).

In sex between men and women, it appears that STIs enhance female to male HIV transmission more than they enhance male to female (Dickerson *et al.,* 1996). This may be because of methodological artefacts, or because women have a greater predisposition to HIV infection in the absence of STIs and therefore any differential effect brought about by STI infection is less. This may suggest that the presence of a genital STI in an HIV negative man, greatly increases the likelihood he will become HIV infected if he is insertive in sero-discordant unprotected anal intercourse. No study has considered this hypothesis.

5.4 INFESTATIONS & HIV TRANSMISSION

Some (mainly parasitic) infections or conditions that are not exclusively sexually transmitted have not been substantially investigated given the reasonable assumption that they are unlikely, biologically, to act as cofactors in HIV infection. Just one study (Craib *et al.,* 1995) has examined pubic lice, intestinal parasites and mononucleosis and found no evidence for an association with HIV infection.

5.5 STIs & HIV INFECTIOUSNESS

No study has shown whether or not HIV infected men are more likely to transmit their infection to other men if they are also infected with another STI. Studies have shown relationships between viral load and transmission, and a number of studies have shown changes in viral load with changes in STIs. Moss *et al.* (1995) found the rate of detection of HIV DNA, in urethral specimens among HIV sero-positive men with gonorrhoea, reduced by half after treatment commenced. Hoffman *et al.* (1996) reported cell-free HIV RNA in semen fell significantly after treatment.

Laga *et al.* (1994) demonstrated in a time series evaluation that monthly testing and treatment for STIs for Zairean female sex workers reduced HIV incidence. These data remain subject to participation bias. There is also evidence from randomised controlled trial evaluations of STI control programmes in Tanzania (Grosskurth *et al.,* 1995) which report reduced HIV incidence. Since this study reported reduced duration of STI episodes but not their incidence, it suggests that behaviour did not operate as a confounding factor.

5.6 HIV & STI SEVERITY

Clottey & Dellabetta's (1993) review suggests that HIV infection is associated with longer duration of STI lesions, more frequent recurrences, and increased treatment failures. There is also evidence that infection with HIV affects the symptoms of some STIs, perhaps encouraging larger lesions (Wasserheit, 1992). Other studies suggest STIs can accelerate the clinical course of HIV through stimulation of CD4 cells, resulting in increased HIV replication (Marlinck & Essex, 1987), and/ or by the immune suppressive effects of STIs (Quinn, 1996).

HIV is thought to act as a cofactor in the transmission of hepatitis C (Bodsworth *et al.,* 1996) and, when the same person is infected with both HIV and hepatitis B, the two infections interact (Adler, 1995). There is no evidence of an inter-relationship between HIV and hepatitis A (Newell, 1995).

Wasserheit (1992) reviewed 83 reports on the effect of HIV on STI natural history and concluded that while HIV infection may act as a cofactor in STI transmission, there is currently no conclusive evidence (Mertens *et al.,* 1990). She also states that HIV probably acts as a cofactor in STI symptom expression and treatment failure (Berry *et al.,* 1987). She concluded that, at a population level, HIV infection is likely to increase the prevalence of some STIs, such as genital ulcers.

6 Epidemiological synergy? Conclusions & implications

The following table summarises the evidence considered in this paper on the potential role of STIs in HIV transmission:

Table 6: STIs which increase the probability of HIV transmission during sero-discordant unprotected anal intercourse between men

When..	The HIV uninfected partner is receptive ('passive')	The HIV uninfected partner is insertive ('active')
The HIV uninfected partner has the STI (increase in susceptibility)		**Syphilis** **Herpes**
The HIV infected partner has the STI (increase in infectiousness)	**Gonorrhoea** **NSU** **Syphilis** **Herpes**	

It should be noted that the absence of evidence regarding other relationships between STIs and HIV transmission is not support for the absence of a relationship. An association may have no evidence to support to it simply because no one has looked for any.

The above table suggests that STIs in HIV uninfected men are likely to increase the risk of insertive anal intercourse far more than they increase the risk of receptive anal intercourse, possibly because receptive intercourse is already so much more likely to result in HIV infection. That is, herpes and syphilis increase the probability of a relatively unlikely event, but not an already likely event.

In addition, the evidence considered here suggests:

- The incidence of herpes, gonorrhoea and NSU among gay men is considerable, although syphilis is rare.
- STIs are most prevalent among homosexually active men in the same geographic areas as is found high HIV prevalence (large, urban centres especially London)
- The evidence for HIV acting as a cofactor in the transmission of STIs is variable, but there is evidence for HIV acting to promote STI symptoms, recurrence and persistence.

These conclusions suggest the following three implications for health promotion programmes designed to reduce the incidence of HIV infection:

- It is likely that HIV prevention resources allocated to reducing STIs among gay men will have a greater impact on HIV incidence in the UK, than they will allocated to reducing HIV exposure in populations very unlikely to be involved in HIV exposure.
- The presumed relatively fewer HIV infections that occur whilst the HIV uninfected partner is insertive, may be reduced by better management of genital herpes among those HIV uninfected men.
- A reduction in the prevalence of gonorrhoea and NSU among HIV infected men (through a reduction in the duration of the infections) is likely to have some impact on HIV infection during sex between men, especially in London. The extent of this impact cannot be estimated from current evidence.

The conclusions also suggest the following implications for health promotion programmes designed to maintain or increase the health of people with HIV infection:

- Considerable health gain is likely to be found in preventing, diagnosing and treating STIs among gay men with HIV infection.

These implications for the integration of HIV prevention and STI prevention programmes arise solely from evidence concerning epidemiological synergy. Debates about the integration of programmes on the basis of affinity of approaches or organisational efficiency (see section 1) will require further considerations of the evidence for and against these arguments.

References

Adler M (1995) *ABC of Sexually Transmitted Disease.* London, BMJ Publishing.

Atkins MC *et al.* (1996) Fluctuations of HIV load in semen of HIV positive patients with newly acquired sexually transmitted diseases. *Br Med J, 313:* 341-2.

Beck EJ, Mandalia S, Leonard K, Griffith RJ, Harris JRW, Miller DL (1996) Case control study of sexually transmitted diseases as cofactors for HIV-1 transmission. *Int J STD AIDS, 7:* 34-8.

Berry CD, Hooton TM, Collier AC (1987) Neurologic relapse after benzathine penicillin therapy for secondary syphilis in a patient with HIV infection. *N Eng J Med, 316:* 1587-9.

Bodsworth NJ, Cunningham P, Kaldor J, Donovan B (1996) Hepatitis C virus infection in a large cohort of homosexually active men: independent associations with HIV-1 infection and injecting drug use but not sexual behaviour. *Genitourinary Medicine, 72(2):* 118-22.

Boulos R *et al.* (1992) Herpes simplex virus type 2 infection, syphilis and hepatitis virus infection in Haitian women with human immunodeficiency virus type 1 and human T lymphotropic virus type 1 infections. *J Infect Dis 166:* 418-20.

Bradford-Hill A (1971) *Statistical evidence and inference in Principles of Medical Statistics.* Oxford, Oxford University Press (9th edition).

CHAPS Strategy Development Group (1998) *Making It Count: a theory, ethics and evidence based health promotion strategy to reduce the incidence of HIV infection through sex between men in England.* London; Terrence Higgins Trust CHAPS Programme (020 7831 0330).

Clottey C & Dallabetta G (1993) Sexually transmitted diseases and human immuno-deficiency virus: epidemiologic synergy. *Inf Dis Clin N America, 7(4):* 753-70.

Cohen MS *et al.* (1997) Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. *Lancet, 349:* 1868-73.

Craib JP, Meddings DR, Strathdee SA, Hogg RS, Montaner JSG, O'Shaughnessy MV, Schecter MT (1995) Rectal gonorrhoea as an independent risk factor for HIV infection in a cohort of homosexual men. *Genitourinary Medicine, 71:* 150-154.

Darrow WW, Cohen JB, French J *et al.* (1987) Risk factors for human immuno-deficiency virus (HIV) infections in homosexual men. *Am J Pub Health, 77:* 479-83.

Deschamps MM, Pape JW, Hafner A, Johnson WD (1996) Heterosexual transmission of HIV in Haiti. *Ann Intern Med, 125:* 324-30.

Dickerson MC, Johnston J, Delea TE, White A, Andrews E (1996) The causal role for genital ulcer disease as a risk factor for transmission of human immunodeficiency virus: an application of the Bradford Hill criteria. *Sexually Transmitted Diseases, 23(5):* 429-40.

Elifson K, Soles M, Sweet M (1989) *Risk factors for HIV infection among male prostitutes in Atlanta.* 5th International Conference on AIDS, Montreal, Canada. Ab no WAP 38.

Elifson KW, Soles J, Sweet M (1993) Risk factors associated with HIV infection among male prostitutes. *Am J Pub Health, 83:* 79-83.

Fauci A (1993) *Immunopathogenic mechanisms of HIV infection: implications for therapeutic strategies.* 9th International Conference on AIDS, Berlin, Germany.

Gilson RJ et al. (1998) Hepatitis B infection in patients attending a genitourinary medicine clinic: risk factors and vaccine coverage. *Sex Transm Infect 74(2):* 110-5.

Grosskurth H *et al.* (1995) Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomized controlled trial. *Lancet, 346:* 530-6.

Hayes RJ, Schulz KF, Plummer FA (1995) The cofactor effect of genital ulcers on the per exposure risk of HIV transmission in sub-Saharan Africa. *J Trp Med Hyg, 98:* 1-8.

Hoffman I *et al*. (1996) *Effects of urethritis therapy on the concentration of HIV-1 in seminal plasma.* 11th International Conference on AIDS, Vancouver, Canada. Ab no. C.903

Holmberg SD, Stewart JA, Gerber RA *et al.* (1988) Prior herpes simplex virus type 2 infection as a risk factor for HIV infection. *JAMA, 259:* 1048-50.

Hook EW, Cannon RO, Nahmias AJ *et al.* (1992) Herpes simplex virus infection as a risk factor for human immunodeficiency virus infection in heterosexuals. *J Infect Dis 165:* 251-5.

Institute of Medicine (IOM) (1996) *The Hidden Epidemic: Confronting Sexually Transmitted Diseases.* Washington, National Academy Press.

Jaffe HW, Choi K, Thomas PA *et al*. (1983) National case control study of Kaposi's Sarcoma and Pneumocystis carinii pneumonia in homosexual men: part 1 epidemiologic results. *Ann Intern Med, 99:* 145-51.

Johnson A *et al.* (1994) *Sexual Attitudes and Lifestyles.* Oxford, Blackwell.

Keet IPM, Lee FK, van Griensven GJP, Lange JMA (1990) Herpes simplex virus type 2 and other genital ulcerative infections as a risk factor for HIV-1 acquisition. *Genitourin Med, 66:* 330-33.

Kingsley LA, Kaslow R, Rinaldo CR *et al.* (1987) Risk factors for sero-conversion to human immuno-deficiency virus among male homosexuals: result from multi-center AIDS cohort study. *Lancet, 1:* 345-9.

Kingsley LA, Armstrong J, Rahman A *et al.* (1990) No association betweenherpes simplex virus type 2 sero-positive or anogenital lesions and HIV seroconversion amongst homosexual men. *J Acquir Immune Defic Syndr 3:* 773-9.

Kiviat N, Rompalo A, Bowden R *et al.* (1990) Anal human papilloma-virus infection among human immunodeficiency virus-seropositive and sero-negative men. *J Acq Imm Def Syndr, 162:* 358-61.

Kreiss JK *et al.* (1986) AIDS virus infection in Nairobi prostitutes: spread of the epidemic to East Africa. *New Eng J Med 314:* 414-8.

Kuiken CL, van Griensven GJP, de Vroome EMM, Coutinho RA *et al.* (1990) Risk factors and changes in sexual behaviour in male homosexuals who sero-converted for human immuno-deficiency virus antibodies. *Am J Epidemiol 132:* 523-30.

Lacey CJN *et al.* (1997) The epidemiology of gonorrhoea in Leeds. *Br Med J 314:* 1715-8.

Laga M *et al.* (1994) Condom promotion, sexually transmitted diseases treatment and declining incidence of HIV-1 infection in female Zairean sex workers. *Lancet 344:* 246-8.

Low N *et al.* (1997) Gonorrhoea in London: the hidden epidemic. *Br Med J 314:* 1719-23.

Marlinck RG & Essex M (1987) Africa and the biology of human immunodeficiency virus. *JAMA, 257:* 2632-3.

Mertens TE, Hayes RJ, Smith PG (1990) Epidemiological methods to study the inter-action between HIV infection and other sexually transmitted diseases. *AIDS, 4:* 57-65.

Moss GB *et al.* (1995) Human immuno-deficiency virus DNA in urethral secretions in men: association with gonococcal urethritis and CD4 depletion. *J Inf Dis, 172:* 1469-74.

Nandwani R *et al.* (1994) Hepatitis A sero-prevalence in homosexual and heterosexual men. *Genitourinary Medicine 70:* 325-8.

Newell A (1995) Hepatitis and HIV: Interrelationship and interactions. *Br J Clin Prac 49(5):* 247-51.

Norton J *et al.* (1997) Repeat HIV testers at a London same-day testing clinic. *AIDS, 11:* 773-81.

Page-Shafer K, Vengelers PJ, Moss AR, Strathdee S, Kaldor JM, van Griensven GJ (1997) Sexual risk behaviour and risk factors for HIV-1 seroconversion in homosexual men participating in the Tricontinental Seroconverter Study 1982-1994. *Am J Epidemiol., 146(7):* 531-42.

Plummer FA *et al.* (1991) Co-factors in male-female transmission in human immuno deficiency virus type 1. *J Inf Dis 163:* 233-9.

Quinn TC, Cannon RO, Glasser D *et al.* (1990) The association of syphilis with risk for human immuno-deficiency virus infection in patients attending sexually transmitted disease clinics. *Arch Intern Med, 150:* 1297-1302.

Quinn TC (1996) Association of sexually transmitted diseases and infection with the human immunodeficiency virus: biological cofactors and markers of behavioural interventions. *Int J STD & AIDS, 7 (Suppl 2):* 17-24.

Schoenbach VJ, Landis SE, Weber DJ, Mittal M, Koch GG, Levine PH (1993) Human immunodeficiency virus sero-positivity in sexually transmitted disease clients in a low prevalence southern state. *Ann Epidemiol, 3(3):* 281-8.

Simms I, Hughes G, Swan AV, Rogers PA, Catchpole M (1998) *New cases seen at genitourinary medicine clinics: England 1996, Communicable Disease Report Supplement 8 (S1).* London, Public Health Laboratory Service.

Stamm WE, Handsfield HH, Rompalo AM, Ashley RL, Roberts PL, Corey L (1988) The association between genital ulcer disease and acquisition of HIV infection in homosexual men. *JAMA, 10:*1429-33.

Tyndall MW *et al.* (1994) Sexual behaviour and perceived risk of AIDS among men in Kenya attending clinic for sexually transmitted diseases. *Clinical Infectious Diseases, 19(3):* 441-7.

Van Raden M, Kaslow R, Kingsley L *et al.* (1989) *The role of ulcerative genital diseases in promoting acquisition of HIV-1 by homosexual men.* 5th International Conference on AIDS, Montreal. Ab ThAO17.

Wasserheit JN (1992) Epidemiologic synergy: Inter-relationships between human immunodeficiency virus infection and other sexually transmitted diseases. *Sex Transm Dis, 9:* 61-77.

Williams DI, Stephenson JM, Hart GJ, Copas A, Johnson AM, Williams IG (1996) A case control study of HIV sero-conversion in Gay men 1988-1993: what are the current risk factors? *Genitourinary Medicine, 72(3):* 193-6.

Wolff H & Anderson DJ (1988) Male genital tract inflammation associated with increased numbers of potential human immunodeficiency virus host cells in semen. *Andrologia, 20:* 2860-4.