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Sexually transmitted diseases (STD) are the burden of sex. Every now and then a new STD emerges, sometimes caused by old and longstanding pathogens. Various influences can cause new, but also old, pathogens to suddenly spread or result in disease. For example, the human herpesvirus 8 (HHV8) has caused numerous AIDS-Kaposi's Sarcoma (AIDS-KS) cases, only after the HIV-1 AIDS epidemic led to widespread immunosuppression. Gradually gaining knowledge about the new diseases and how they arose has opened ways for control. Control measures for STD have focussed on behavioural prevention programs and treatment, and efforts to develop vaccines. A lot can be reached with such measures, as is shown by how well HIV-1 has been tackled in some countries in some time periods. But in most cases the success of control is limited and 'maintenance measures' prove to be essential. These entail continuous development and application of more efficient strategies and certainly depend on continuous monitoring of STD and of the factors causing STD to spread, including specific risky behaviours.

In industrialized countries, homosexual men have been disproportionately affected by HIV-1 and other STD, such as gonorrhoea and syphilis. This thesis focuses on homosexual men in industrialized countries, describing current trends in STD and related sexual risk behaviour and the role of STD control measures. Along with the epidemiology of HIV-1, the studies presented focus on the transmission and symptoms of HHV8 infection and on several aspects of the herpes simplex virus (HSV).

**HUMAN IMMUNODEFICIENCY VIRUS**

After the HIV-1 AIDS epidemic struck the homosexual community in the early eighties and unprotected anal sex was recognized as the most important route of HIV-1 transmission, prevention campaigns were set up to reduce this high-risk sexual behaviour.\(^1\)\(^-\)\(^3\) In the following years, the incidence of HIV-1 and other STD declined drastically among homosexual men, remaining relatively low and stable with some fluctuation. In the early to mid-nineties, a slight increase in sexual risk behaviour and STD incidence was noted in Amsterdam as well as in other cities,\(^2\)\(^,\)\(^4\)\(^-\)\(^6\) but levels declined again only a few years later. Recently, several cities in the US and Europe have again reported a rise in STD among homosexual men, but it is now much steeper than previously.\(^7\)\(^-\)\(^17\) Among homosexual visitors of the Amsterdam STD clinic, since 1998 the number of cases of rectal gonorrhoea and syphilis has yearly more than doubled. These STD are considered to be suitable markers for unprotected anal sex,\(^18\) and as expected, their rise was accompanied by a rise in sexual risk behaviour (Chapter 1.1). These trends are still continuing in 2001 (unpublished data), pointing to a sustained increase in contrast to the earlier short-lived increases. Studies in other industrialized countries report similar findings.\(^19\)

**WHAT COULD BE CAUSING THE INCREASE IN SEXUAL RISK BEHAVIOUR?**

In addition to a wide range of sociodemographic factors, such as education and age, and psychological conditions, such as depression, that have repeatedly been shown to influence the sexual risk behaviour, some emerging factors may account for recent trends.\(^20\)\(^-\)\(^32\) The mid-nineties were marked by the availability of revolutionary new treatment possibilities in HIV-1 infection, called highly
active antiretroviral therapy (HAART). Popular beliefs about HAART and treatment advertisements with appealing but unrealistic images of 'healthy & happy' HIV-1 positive patients, as well as testing of vaccine candidates and the availability of post exposure prophylaxes and viral load monitoring could all influence the perceptions of risk and consequences of HIV-1 infection, affecting sexual behaviour. The growing use of the internet is also proposed to play a role in the recent trends in sexual behaviour and STD, because the internet offers a fantastic network for enhancing sex-seeking efficiency.

Thus far, most attention has been paid to the influence of HAART on recent trends in sexual risk behaviour. People are no longer dying from AIDS, enlarging the pool of people living with HIV-1. The mere availability of such potent anti-HIV-1 treatment holds new promise for anyone. Though homosexual men are on the whole quite realistic about the threat of HIV-1 and the effect of treatment, more optimistic visions have indeed been associated with risk behaviour.

Specific aspects of the actual use of HAART were also associated with unprotected sexual activity, as indicated by our studies among older HIV-1 infected homosexual men (Chapter 1.1 and 1.2). A higher level of unprotected anal sex with casual partners was observed in patients who had experienced their first HAART induced improvements, i.e. after the first switch from detectable to undetectable viral load and after the first increase in CD4 cell counts to above 350 (Chapter 1.1). Though follow-up after HAART was short in this study, results suggest that sexual risk behaviour first increased but decreased again with sustained virological and immunological improvements. The underlying motives for engaging in unprotected anal sex in the context of HAART-use might reflect a short-term and transient euphoria due to the success of treatment, i.e. feeling better physically and mentally. Another aspect of HAART-use became evident in a separate study in which persons taking HAART for a longer time were interviewed about their sexual well-being and behaviour (Chapter 1.2). Half of the men using HAART had developed lipodystrophy, a side-effect of HAART that is characterized by clearly visible physical changes in fat distribution. These men reported no change in the pattern of condom use but reported a decrease in their sexual activity and well being during this side effect. Other investigators have found that HAART-experienced individuals, and especially those with signs of lipodystrophy, report a decrease in sexual interest and increase in sexual dysfunction. Interestingly, in contrast to the men in Chapter 1.1 who used HAART for a short-time, those treated for a somewhat longer period had on average decreased their sexual activity during treatment. Those who had experienced lipodystrophy during treatment additionally reported an increase in condom use.

The general tendency is that HAART improves quality of life, though it also brings side-effects. Supposedly psychological and physical effects differ in the various stages of treatment, and in turn can affect the sex-life. There seems to be clear evidence from Chapter 1.1 and international studies that some aspects of HAART-use are associated with increased sexual risk behaviour and having STD. But, since using HAART is a dynamic process with positive and negative consequences, it is still difficult to fully comprehend to what extent actual HAART use accounts for the general rise in STD and risk behaviour observed among HIV-1 infected men. More focus is needed on the different facets of being on treatment when investigating the effect of HAART.
ARE WE HAVING A NEW EPIDEMIC: TRENDS AND PREDICTION MODELS

Because of its potential to reduce the HIV-1 infectiousness in the population on treatment, HAART could bring down HIV-1 incidence.45-47 Ironically however, HAART may well be causing the HIV-1 epidemic to surge in the homosexual community if the treatment indeed triggers sexual risk taking. Two mathematical models of homosexual men (living in San Francisco and Sidney) showed that rises in such behaviour of 10 and 70 percent, respectively, would counter the positive effects of HAART on reducing the HIV-1 incidence in these cities.46,47 To predict the course of the HIV-1 epidemic in the HAART era by such models, several factors need to be considered, such as the proportion HIV-1 infected persons on treatment, the infectiousness of the people treated and the rate of sexual risk behaviour. Additionally, more detailed information could be used, including the type of sexual partners (high or low risk), emergence of treatment resistant strains in the population or rising STD rates. At the moment, efforts are being undertaken to build a prediction model for the HIV-1 epidemic among homosexual men in Amsterdam based on the available epidemiological and socio-demographic data. By constructing such a model, we aim to understand which prevention strategy or combination of strategies (e.g. treating more people, enhancing behavioural campaigns) would be most effective in reducing the HIV incidence.

The strongly increasing trends in sexual risk behaviour and STD have already warned of a resurgent HIV-1 epidemic, which had been at a low endemic level for quite some years now. Incidence was quite stable in young homosexual men participating in the Amsterdam Cohort Study (Chapter 1.1 and 1.3). However, we have demonstrated a rising HIV incidence in homosexual men who attend an STD clinic in Amsterdam. Strikingly, the increase was only evident in older clinic attendees and not in the young. This finding agrees with rising syphilis rates in older homosexual men. Since STD clinic attendees are at highest risk for HIV infection, any trends observed in this group do not necessarily imply similar increases in the ‘general homosexual’ population. However, trends detected in such a high-risk group could be the first indicators of a general change. Moreover, an STD clinic provides services to a population who may have the majority of HIV-1 infections (being a high-risk group). Thus our findings should prompt immediate preventive action to limit further spread of HIV. More research is needed to understand why increases occur especially in the elderly.

PREVENTING THE SEXUAL TRANSMISSION OF HIV-1

There is no doubt that the development of an effective HIV-1 vaccine is crucial in controlling the HIV-1 epidemic worldwide. However, the introduction of vaccines with suboptimal efficacy could intensify the epidemic if risky sexual behaviour rose due to the perception that vaccination conferred full protection from infection.48,49 Similarly, great advances in treatment were made with the development of HAART, but it is not accessible to most of the world and possibly increases the sexual risk behaviour to whom it is available. Thus, vaccines and treatment are not (yet) fully efficient in controlling the HIV-1 epidemic, and in conjunction we need other methods. Such strategies for preventing the sexual transmission of HIV-1 have focussed on encouraging the use of condoms and treating STD.49,50 Prevention messages for homosexual men have generally promoted safe sex and have not been substantially reviewed in light of changing times. The recent increases seen in risk behaviour and STD call for renewed
preventive action. The 'old' and general message of safe sex needs to be reinforced again for the public. The studies in this thesis as well as other international findings clearly indicate specific target groups that would benefit from prevention messages and methods better tailored to their situation.

**THEMES AND TARGET GROUPS IN CURRENT HIV-1 PREVENTION**

The availability of HAART sheds new light on several issues regarding HIV-1 infection, such as knowledge of one's own serostatus. Serostatus awareness benefits the HIV-1 infected individual by providing the opportunity to consider or start treatment. The larger the proportion of HIV-1 infected persons who are successfully treated, the lower the infectiousness in that population, an important factor in reducing HIV-1 incidence. Several reports show that the share of seropositives with unknown serostatus is still high. Up to 1998, around one third of all HIV-1 infected Americans were unaware of their serostatus.\(^{51,52}\)

Of HIV-1 seropositive homosexual men attending the Amsterdam STD clinic from 1996 to 1999, 55 percent were unaware of their infection. Of special concern in the transmission of HIV-1 is the individual who is recently infected, because he or she is highly infectious (having high HIV-1 RNA levels), while being unaware of the infection (Chapter 1.3). It is thus important to increase the proportion of HIV-1 infected persons who know their HIV-1 status and to detect infections as early as possible.

Until recently, people with HIV-1 infection and AIDS have seldom been the target of prevention programs. Several countries, including the Netherlands (see next section) have now acknowledged the need to reach them with new and targeted prevention strategies. To give only two examples, the United States, Centers for Disease Control, have launched a new approach, called SAFE: serostatus approach to fighting the epidemic.\(^{52}\) This program aims to increase the number of HIV-1 infected persons who know their HIV-1 status and also to increase the use and quality of health care and prevention services. Special efforts are made to increase the number of infected individuals who adopt and sustain HIV-1 and STD risk reduction behaviour. In England the Department of Public Health has produced a framework for preventing STD, with special emphasis on improving social and health care for people living with HIV-1.\(^{53}\)

The serostatus approach involves prevention messages specifically designed for HIV-1 seropositives, who may be taking HAART. The studies described in Chapter 1.1 and 1.2 and other studies in this field show that using HAART in itself, does not have a general influence on sexual behaviour and well being, but it covers a dynamic process having various influences in the diverse stages of treatment. The different aspects of HAART use should be recognized by health care providers and prevention workers in order to provide tailored counseling and prevention messages. For example, persons being treated with HAART need to know they still can infect their partners, even when the virus can no longer be detected in the blood. Today, it is still not easy for HIV-1 infected people to discuss their sexual well being and life style, for example with their clinician, while HAART-use may have severe consequences on a persons sexual life. Prevention should thus create an environment in which such issues can be discussed.\(^{54}\) Our studies suggest other target groups to receive prevention counseling, such as persons in whom HIV-1 RNA levels are high and increasing when not taking HAART (Chapter 1.1). Likewise, those persons who tried and failed treatment (having increasing HIV-1 RNA levels) should not be excluded

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from counseling. More detailed research is needed to clarify the reasons why these and other groups refrain from the use of condoms.

In general, among HIV-1 positive and negative men, HIV-1 prevention work needs to tackle the misconceptions concerning HAART as well as to enhance the general motivation, or responsibility, to practice safe sex. Further, a more aggressive approach to STD control is needed. It is essential that along with HIV-1 infection, prevention programs address other STD, and that STD awareness and treatment are stimulated. Too often, the acquisition of STD other than HIV-1 infection is still considered by persons at risk to be a minor problem and merely an inevitable consequence of a pleasant activity. Yet STD can cause significant morbidity, especially among persons who are immunocompromised, and STD can enhance HIV-1 transmission and acquisition of infection. For example, prospective epidemiologic studies show that gonorrhoea and genital herpes are associated with an increased risk of acquiring HIV-1 infection. Virologic studies show that increased concentrations of HIV-1 are found in lesions caused by urethral gonorrhoea and genital herpes. Possibilities for specific control of HHV8 and HSV are discussed below.

CURRENT PREVENTION PROGRAMS IN THE NETHERLANDS
In response to the increase in STD, the organization responsible for developing prevention programs for homosexual men in the Netherlands, the SAD Schorer Stichting, has also developed plans to intensify efforts to prevent HIV-1 as well as other STD and to give special attention to HIV-1 positive persons. Also the need for a more systematic feedback of the STD rates from the clinic to the prevention workers is recognized, in order to trace foci of infection more quickly. To promote screening and stress the need for treatment, flyers are being distributed among homosexual men to provide information about HIV-1 and other STD. Condoms are distributed free of charge at 'sex venues' for homosexual men, where STD counseling is also available (Personal communication B. Bakker, SAD Schorerstichting). Using the internet as a preventive tool is being extensively explored at the moment by municipal health services in several cities. The University of Maastricht is developing an evidenced-based behavioural prevention program specifically directed towards HIV-1 positive homosexual men. The Amsterdam STD clinic is offering voluntary HIV-1 tests for all clinic attendees and intends to broaden its STD care to various settings to meet the increasing need for care.

It is important to realize that encouraging HIV-1 testing needs to be coupled directly to provision of adequate treatment and prevention services. Reducing the number of HIV-1 positives who are unaware of their infection implies enlarging care facilities and intensifying prevention efforts. Unfortunately, it appears to be difficult to actually implement services, such as creating opportunities for HIV-1 positives to discuss sexual health issues with clinicians. Though the need for this is generally considered to be important, little has been accomplished. It is imperative that prevention programs for HIV-1 positives are not only put on the agenda, but that more efforts are undertaken to develop and implement such programs.
CONTINUE MONITORING
Monitoring of certain behaviour that puts one at risk of acquiring or transmitting HIV-1 or other pathogens is important, not only to elucidate behavioral processes and their role in transmission, but also to detect trends early enough to take action. Cohort studies are one of the tools in such monitoring. Useful additions of gathering behavioural data can be obtained by population surveys. Several possibilities are viable, as long as the data are valid and comparable over calendar time when examining trends. Along with sexual behaviour, we should of course keep monitoring the incidence of HIV-1 and other STD. Estimates of new HIV-1 infections can be extremely valuable for evaluating the current risk of infection. In the past, sources of information on HIV-1 infection were AIDS surveillance data coupled with methods such as back calculation, which allows one to reconstruct historical HIV-1 incidence from the number of reported AIDS cases. In the HAART era, back calculation has become virtually impossible because AIDS trends no longer reflect the natural history of the disease. Also HIV-1 surveillance systems that measure HIV-1 prevalence have been used to shed light on the time trends, although stable or decreasing trends in prevalence can easily mask increases in the incidence (Chapter 1.3). Despite limitations such as biased study populations, cohort studies with repeated measurements remain useful sources of information about incidence. But, to achieve a comprehensive view of the HIV-1 incidence in a population, it is important to study and compare various sub-populations, such as the high and low risk groups (Chapter 1.1 and 1.3). Recently, development of the serologic testing algorithm for recent HIV-1 seroconversion (STARHS) has made it possible to estimate the HIV-1 incidence within a cross-sectional survey. When coupled to existing surveillance systems, this approach provides a valuable addition to incidence estimates based on cohort studies. This STARHS is based on the slow antibody response in HIV-1 infection. Seropositive samples are tested with a less sensitive ('detuned') HIV-1 assay and samples non-reactive in this less sensitive assay are classified as being from persons who are recently infected. For now, the test is not validated for non-B subtypes and can therefore not yet be used in evaluating the spread of non-B types in industrialized countries. More important, it cannot yet be used in most African countries, where AIDS is a huge problem. But efforts are underway to develop a valid non-B test. Meanwhile, several countries, including the Netherlands, are planning to apply this assay in subpopulations where HIV subtype B prevails.

HUMAN HERPESVIRUS 8
In 1995, HHV8 was discovered to be the necessary cause for one of the most common AIDS defining illnesses among HIV-1 infected homosexual men, namely KS. Several methods for serologic detection of antibodies against HHV8 have been developed. However, there is no gold standard for HHV8 (the virus cannot be reliably cultured), and therefore tests remain imperfect in the sense that they lack optimal specificity and sensitivity. This shortcoming influences results of epidemiological studies because of misclassification of the HHV8 test results and thus cannot be ignored when designing such studies and interpreting the findings. For example, in situations with high prevalence of the disease under study, suboptimal specificity in combination with suboptimal sensitivity will most likely lead to underestimation of the associations, at least when the
misclassification of the outcome is unrelated to the risk factors of interest. As shown in Chapter 2.2, the percentage of the defined cases in the study that are true cases (specificity) becomes more and more important when the prevalence of the true cases in the study is low. In situations of very low prevalence, the number of false cases can exceed the number of true cases and can lead not only to underestimated risks but to spurious associations (Chapter 2.2). Lacking an optimal test to identify HHV8 antibodies, various serological assays are used, which accounts for a substantial part of the variation in prevalence findings across studies. However, the relative distribution of HHV8 among HIV-1 risk groups and geographical areas was comparable in most studies. Distribution findings were confirmed by findings in the Amsterdam Cohort Studies, with HHV8 prevalence and incidence being high among homosexual men and among persons with Mediterranean nationality, but low among drug users. Other studies show that HHV8 prevalence is comparably low in heterosexuals and in children within a defined geographical region.67-71

CLARIFYING HHV8 TRANSMISSION, A CONTINUING CHALLENGE
The distinct distribution of HHV8 in HIV-1 risk groups and geographical areas continues to puzzle epidemiologists, though it has also revealed some secrets of HHV8 transmission, such as being sexual in homosexual men. Studies performed in HHV8-endemic countries suggest that infection with HHV8 occurs within families and is associated with conditions of close contact and crowding.69,72-74 These correlates are commonly noted also for many other viruses, including hepatitis B, HSV, and EBV, and could account for the observed geographical gradient. Childhood transmission appears to be rare in the United States and Northern-Central Europe but does occur in countries where HHV8 is more widespread, such as African and Mediterranean countries.69,70,72,75-79 Vertical transmission of HHV8 seems to be rare.

In Chapter 2.2 we have provided reasonable evidence that HHV8 is not spreading among drug users in Amsterdam and that injecting drug use is not a convincing route of transmission. A virus needs a route of transmission to sustain its presence after introduction, and such a route was apparently present among homosexual men, who have a continuously high prevalence and incidence. These continuously high levels of infection were in contrast with initial decreases in HIV-1, gonorrhoea, syphilis and unprotected anal sex observed in the early eighties. The population of drug users has consistently showed a low and stable prevalence over more than 15 years of monitoring. HHV8 is likely to be occasionally brought into this group by drug users who had sex with homosexual or bisexual men and by drug users coming from HHV8 endemic areas. A very common behaviour in this group and known spread HIV-1, HBV and HCV, namely, injecting drugs with shared equipment, cannot result in a likewise spread of HHV8. International studies demonstrate some evidence of HHV8 infection by blood, blood-products, or donor grafts, though most agreed that transmission by blood must be very rare.80-85 There is now consensus that at least among homosexual men, transmission of HHV8 is sexual, and therefore in this group AIDS-KS can be considered an STD. However, the specific mechanism of sexual transmission remains in object of considerable debate. Some but not all earlier studies on the relation between KS and sexual practices found an association between oral-anal sex and this AIDS-defining event. Cross-sectional studies have demonstrated an association
between the presence of HHV8 antibodies and anal-genital sex, oral-anal sex, or deep kissing with an HIV-1 positive partner. The study in Chapter 2.1 is still the only large prospective study to associate a specific sexual technique, namely oral-genital sex, with HHV8 seroconversion. Longitudinal studies of viral shedding showed that HHV8 is not shed substantially in semen or rectal tissue, but is persistently found in the oral cavities of some persons.\textsuperscript{86} The symptoms associated with primary infection, especially sore throat are consistent with HHV8 infection in the oropharynx (Chapter 2.3). Oral-genital sex is a common practice among homosexual men, as is kissing. Thus if saliva is a carrier for HHV8, it may transmit inefficiently. Our HHV8 study may well have underestimated the risk of the sexual techniques we examined, and surely did not rule out HHV8 transmission by multiple carriers and transmission routes. However, HHV8 may even be less easily transmitted by receptive ano-genital or insertive oro-anal sex for example, since little or no virus is detected in semen or feces when compared to saliva.\textsuperscript{87}

Cross-sectional studies made it clear from the beginning which techniques were associated with sexual transmission of HIV-1.\textsuperscript{88} Later on, prospective studies confirmed these risk factors and demonstrated that oral-genital sex played only a very limited role in HIV-1 acquisition. In a commentary on the study of Chapter 2.1 researchers noted that associations of a large-order of magnitude (as observed for HIV-1) withstand a certain degree of bias (such as that caused by misclassification) and thus can still be detected.\textsuperscript{89} Since there is so much discrepancy in the results of HHV8 studies, the associations sought for in HHV8 transmission may thus be of low magnitude. In order to detect subtle associations, reducing bias as much as possible should be a priority when designing future studies, e.g. by using optimal serological assays, prospective information, and detailed measuring of variables.

Aside from the study design, other explanations may also account for the differences in the risk factor findings obtained in various countries and populations. It might be the case that in some subpopulations, such as homosexual men, multiple routes exist or that a certain transmission route (e.g. via saliva or blood) is more efficient in a certain population due to facilitating factors, such as higher virus titers. In addition, the public health importance of an association must be evaluated separately for each population or geographical area. A given transmission route may account for more infections in a population of high HHV8 endemicity than in a population of low endemicity, because the chance to encounter the virus is simply greater.

**CAN WE TAKE MEASURES YET TO 'CONTROL' HHV8?**

Because current HHV8 serological assays are suboptimal, it is impossible to study HHV8 in low risk settings adequately and in a simple manner. Also for studies in high risk settings, where misclassification can lead to biased results, a good HHV8 serological assay is essential. We are still in the stage of gaining knowledge, but we can use the information already available. The possibility of HHV8 transmission by blood is an important issue to consider because of its potential consequences for blood bank screening. From our study we do not detect a need to screen blood donors in the Netherlands. Transmission by blood is probably very rare in countries of low endemicity, and high-risk groups for HIV-1 (and thus for HHV8) are already being excluded from donation. Nevertheless, by the time a better test for HHV8 becomes available, it may be
necessary to confirm our findings in blood donors and investigate blood transfusion-related HHV8 transmission in the Netherlands. Although its sexual transmission route or routes are not completely understood, we know that HHV8 needs a compromised immune system in order to cause KS. For HIV-1 positive individuals, this fact offers extra motivation to practice safe sex, including safe oral sex, to minimize the chance of HHV8 infection and development of KS. Additional studies are needed to investigate sexual transmission routes and the role of deep kissing as well as non-sexual transmission routes causing HHV8 to infect children in HIV-1 endemic African countries.

There are several treatment possibilities for KS, which responds very well to HAART. The study in Chapter 1.3 is one of the first to examine the symptoms of primary HHV8 infection. In HIV-1 negative men, primary infection was characterized by a mild flu-like illness that could be used for identifying HHV8 seroconverters. However, this flu-like illness cannot be an efficient tool for diagnostic purposes, because it occurred in only a small proportion of HIV-1 negative men, and among HIV-1 positive men, none of the investigated symptoms were substantially elevated during HHV8 seroconversion. Research in this field is still very scarce, and clinical studies are needed to further characterize primary HHV8 infection.

**HERPES SIMPLEX VIRUS TYPE 1 AND TYPE 2**

With development of type specific-serologic tests for HSV, it became possible to easily investigate type 1 and type 2 in epidemiologic studies. In Chapter 3, we demonstrated that prevalence of both HSV1 and HSV2 was substantially lower among young homosexual men in 1995-1997 than in 1984-1985. This decrease was in line with decreasing sexual activity and unprotected anal sex among homosexual men following massive campaigns targeted on the prevention of HIV-1 infection. Though childhood non-sexual transmission of HSV1 is still the most common mode, it is becoming less common in industrialized countries. Sexual transmission of HSV1 still plays a minor role but seems to be increasing. More often than in the past, HSV1 is the cause of genital herpes, and like HSV2, is on its way to becoming a cause of STD among homosexual men. This trend is illustrated by findings among homosexual attendees of the Amsterdam STD clinic, where the share of HSV1 found in genital herpes lesions increased in the last decade from 25 percent to 35 percent (personal communication H. Fennema, STD clinic Amsterdam, 2000).

**CURRENT POSSIBILITIES FOR HSV CONTROL**

An impressive number of studies have examined the relationship between infection with HSV2 and HIV-1, clearly showing that the two epidemics enhance each other. However, well designed prospective studies among homosexual men are scarce and need in particular to detail the influence of HSV infection on HIV-1 seroconversion when controlling for sexual practices. For this and other reasons, stored sera from the Amsterdam Cohort Study among homosexual men are now being tested for HSV1 and HSV2 in a temporal fashion, using a comparable testing strategy as described for HHV8 (Chapter 2).
Consistent condom use may help to reduce the risk of HSV infection by covering exposed or susceptible mucous membrane and skin. In industrialized countries, symptomatic treatment is available and is most effective when applied at the first signs of beginning lesions. The continuous use of antiherpes drugs may even reduce the risk of HSV transmission by decreasing the quantity of asymptomatic viral shedding. Among the 532 young homosexual men in our study, 74 percent had antibodies to any type of HSV (33 percent of 532 men had antibodies to HSV2). But only 7.5 percent of these HSV infected men (and 12.8 percent of the HSV2 infected men) reported a five-year history of ano-genital herpes (Chapter 3). The manifestations of genital herpes vary widely among individuals and even among episodes in the same individual. An ‘asymptomatic’ infection is often symptomatic infection that goes unnoticed. Asymptomatic transmission is important, because infected individuals with no apparent symptoms constitute a large reservoir for infection. Asymptomatic transmission is amenable to methods of control through appropriate diagnosis, counseling, and treatment.

It is thus crucial to identify the HSV carrier by increasing the general awareness of symptoms. Perhaps, in some settings, routine laboratory HSV testing might be considered. Especially in African countries, there is a great concern about the effects of HSV (genital ulcerations, neonatal herpes) and its potential to boost the HIV-1 epidemic. But since anti-herpetic treatment is often unavailable or too costly there, considerable interest has been shown in the development of a vaccine to prevent acquisition of genital herpes. No effective vaccine is yet available, though clinical trials are in preparation.

**SUMMARIZING REMARKS**

Many times, we have seen STD suddenly emerging or re-emerging because of new introductions of underlying pathogens or increases in factors facilitating spread of a pathogen, such as increases in sexual risk behaviour. Another cause is changing transmission modes, as is exemplified by HSV1, which appears in recent years to have become more and more sexually transmitted among homosexual men. In the industrialized world, past experience has proved it is possible to quickly bring down the incidence of HIV-1, the most threatening infection of the last two decades. Though not all prevention methods have been equally successful, primary behavioural strategies have played a crucial role in reducing HIV-1 infections and other STD. Now we face a new challenge with STD increasing again and the HIV-1 epidemic on the verge of resurgence. It is only sensible to renew prevention efforts and target especially HIV-1 positive individuals who hold the key in limiting the spread of HIV-1. Continuous monitoring of risk behaviour and the incidence of STD and HIV-1 is essential to keep track of the current risk of these infections. Cohort studies are excellent monitoring tools and hold the potential to discover new transmission routes and new STD, such as HHV8 infection, and their role in morbidity. To learn more about this very intriguing HHV8, a serological assay is needed that is adequate and simple to apply in both low- and high-risk settings. Experiences with HHV8 have underlined the inter-reliance between epidemiology and other research fields, such as virology, immunology and sociology. Continuing group effort is therefore important, as exemplified by implementing the STARHS or ‘detuned’ assay, a novel diagnostic method, able to use a single serum sample for
detecting recent HIV-1 infections of subtype B. This extremely valuable tool in
the monitoring of HIV-1 enabled us to demonstrate a rising HIV-1 incidence
among homosexual men, and should, as soon as it is proven to be valid in non-B
HIV-1 subtypes, be put to wide use.

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