Epidemiology of HIV-1, HHV-8 & HSV among homosexual man
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GENERAL INTRODUCTION
The research that comprises this thesis has been performed predominantly with data from the Amsterdam Cohort Studies, founded in 1984. Although set up to investigate the human immunodeficiency virus (HIV) and Acquired Immuno Deficiency Syndrome (AIDS) in homosexual men and drug users, these studies are also suitable to study the epidemiology and natural history of additional viruses. In this thesis, both prospectively and retrospectively gathered data are utilized to investigate time trends in occurrence and modes of transmission of several sexually transmissible pathogens, including HIV, as well as related trends in sexual behaviour. The research is focussed mostly on homosexual men and on conditions in industrialized countries.

This chapter provides background information on the HIV AIDS epidemic and the pathogens studied for this thesis. It highlights the value of cohort studies for such research and outlines the scope of this project.

**HIV AND AIDS**

Two decades ago, in 1981, the first clusters of cases of Kaposi's sarcoma (KS) and *Pneumocystis carinii* pneumonia were described in the United States. They appeared to be manifestations of a newly recognized immunodeficiency syndrome, later named AIDS. A few years later, the virus causing AIDS was discovered and called HIV. Cross-sectional and prospective studies were set up to study HIV transmission and the natural history of disease. These studies showed that HIV could be transmitted by unprotected sex with someone who is HIV infected, by exposure to contaminated blood products, and by breastfeeding. Now AIDS is a global pandemic with 24 million deaths and an additional 40 million people infected with HIV, mostly striking developing countries with a burden of 28 million infected people. Whereas in Africa heterosexual transmission predominates, in industrialized countries, HIV is transmitted largely among homosexual men and injecting drug users, although the share of heterosexual transmission is increasing strongly.

In HIV infections the type 1 of the virus predominates. In a person infected with HIV-1, the estimated median time to development of AIDS was about 9 to 11 years, at least before treatment became available. The fortunate availability of anti-HIV-1 treatment in industrialized countries has had a major impact on the natural history of HIV-1 infection. Since treatment was initiated with Zidovudine, the first agent found to affect HIV-1 replication in vivo, new methods have been developed. In July 1996, a new and very powerful combnation therapy, consisting of at least three different agents, became generally available in the US and Europe: suitably called highly active antiretroviral therapy (HAART). It has greatly improved survival and quality of life among HIV-1 infected individuals. After its successful use, HIV-1 RNA reaches very low levels in the blood, and the immune system seems to recover. Viral suppression by HAART is 10 to 100 times more effective than viral suppression by Zidovudine alone.

While the AIDS epidemic has shaken the world, the availability of potent treatment possibilities in the industrialized countries has provided reassurance. Indeed, the general notion in these areas has been shifting, with HIV-1 infection becoming a manageable and chronic disease. However, the long-term effect
results of HAART remain uncertain. Coinciding its promises, the new therapies have important drawbacks: a high pill burden and extreme side effects.\(^9\) Development of new treatment methods, easier to adhere is a dynamic and fast progressing area.

Along with all research efforts, behavioral prevention campaigns were launched at the beginning of the HIV-1 AIDS epidemic, focused first on reduction of risky sexual behaviour and then on reduction of risky drug using behaviour.\(^10\) In industrialized countries, risk behaviour as well as the incidence of HIV-1 and other STD decreased drastically in following years.\(^11\) These encouraging trends have been demonstrated by cohort studies, which are especially valuable in that they combine behavioural information with measuring the HIV-1 incidence. However, cohort studies may be biased in that they represent a self-selected (eg. low risk) group and not the entire population in which the majority of new infections are occurring. Recently, a laboratory method was developed which distinguishes recent from longer-standing HIV-1 infections by using only a single serum sample,\(^12\) making it possible to investigate incidence outside cohort studies. This serologic testing algorithm for recent HIV-1 seroconversion (STARHS) is based on the slow antibody rise that occurs after HIV-1 infection, causing HIV-1 seropositive samples (as determined using a sensitive HIV-1 assay) from recently infected persons to be non-reactive in a less sensitive ('detuned') HIV-1 assay. Its development is a major step forward in tracking the incidence of HIV-1, because it is a simple and low-cost method that can easily be optimized when coupled to existing surveillance systems, such as HIV-1 prevalence surveys at local STD clinics.

In addition to HIV-1, several other sexually transmissible pathogens can cause human disease (STD). The symptoms often worsen when their infection is accompanied by HIV-1 infection, as when *Neisseria gonorrhoeae* or *Treponema pallidum* cause non-ulcerative or ulcerative genital disease. The two following sections will focus on the human herpesvirus 8 (HHV8) and herpes simplex viruses (HSV), the other sexually transmissible pathogens studied in this thesis.

**HUMAN HERPES VIRUS TYPE 8**

Among HIV-1 infected homosexual men, KS has been one of the most common of all AIDS defining illnesses with a share of 22 to 29 percent.\(^13\) Other variants of this vascular tumor described among HIV-1 uninfected people include classic KS, a rare form found in elderly Mediterranean men and Jewish people from eastern Europe; African KS found in young black adults and children in equatorial Africa, and post-transplant KS, seen in patients who have received immunosuppressive therapy due to organ transplantation or other conditions. KS may develop in the absence of immune deterioration, but most cases occur when the immune system is affected, as by HIV-1, advancing age, or organ transplantation. AIDS-KS is more prevalent among homosexual men than among other HIV-1-infected populations, such as drug users or heterosexuals. Based on this risk-group distribution, a sexually transmitted agent besides HIV-1 was suspected to contribute to development of this tumor.\(^14\) In 1995, a new human gamma herpesvirus was discovered: the human herpesvirus type 8 (HHV8), also named kaposi's sarcoma associated herpes virus (KSHV).\(^15\) When cross-sectional studies
demonstrated in HIV-1 infected individuals an association between KS and the presence of HHV8, several cohort studies on HIV-1 and AIDS screened their stored sera for antibodies against this new virus. Though serological assays to detect HHV8 are still suboptimal, demanding cautious interpretation of the results, such application has gained quite important insights. It was shown that HHV8 causes indeed KS in HIV-1 infected individuals, and those persons who seroconvert for HHV8 after HIV-1 infection are at higher risk to develop KS than those who seroconvert for HHV8 before HIV-1 infection. In addition to KS, HHV8 is strongly associated with body cavity-based lymphomas and Castleman’s disease. The only other human gamma herpesvirus, the Epstein Barr virus (HHV4), is associated with lymphomas and nasopharyngeal carcinoma.

Human herpesvirus 8 shows a distinct geographical distribution, which mirrors the geographical distribution of KS before the AIDS era. Prevalence of HHV8 is low in most of Asia, North America, and northern Europe, but higher in Mediterranean and eastern European countries. The highest prevalence has been found in central and southern African countries. In the HIV-1 infected population, HHV8 infection shows a distinct risk-group distribution, paralleling the AIDS-KS distribution; prevalence of HHV8 is low among heterosexuals or drug users but high among homosexual men. There is considerable debate as to how HHV8 is transmitted. It is presumed that, at least among homosexual men, HHV8 is predominantly transmitted sexually, but the precise mode is unclear. Among other groups, such as children, drug users or African populations, transmission routes might be different.

HERPES SIMPLEX VIRUS TYPE 1 AND TYPE 2

Herpes simplex virus type 1 and type 2 (HSV1 and HSV2) belong to the subfamily of alpha human herpesviruses. Transmission of HSV occurs by intimate contact with someone who is shedding the virus at a peripheral site, mucosal surface, in genital or oral secretions. Infection occurs via inoculation of virus on mucosal surfaces or through small cracks in the skin. After a person is infected with HSV, the virus remains present in the host and can cause primary and recurrent symptoms. These include ulcerations, blisters or sores around the genitals (genital herpes) or mouth (herpes labialis or ‘cold sores’). Shedding of virus occurs not only when symptoms are present but also during asymptomatic periods after infection. Although Treponema pallidum, for example, can cause genital ulcerations, infection with HSV is the most common cause of such lesions. Genital herpes is caused mostly by HSV2 although HSV1 is now increasingly found in the genital lesions. Herpes labialis is mostly caused by HSV1 infection. Primary HSV infection symptoms tend to be more severe than recurrent symptoms. Moreover, genital herpes caused by HSV2 is more severe, and the recurrence rate is higher, than genital herpes caused by HSV1. Symptoms of genital herpes are more severe in HIV-1 infected individuals.

The public health impact of genital herpes is increasingly recognized. In addition to genital lesions, infection with HSV can result in encephalitis and neonatal herpes. Herpes simplex virus type 2 seropositivity increases susceptibility to HIV-1 infection, and HSV2 infection may increase the infectiousness of HIV-1. A study among HIV-1 infected men showed that in genital ulcers caused by HSV2, HIV-1
was consistently detected (at a high rate), whether the plasma HIV-1 titers were high or low. Moreover, HIV-1 infection increases the susceptibility to HSV2 infections, and also the rate of shedding, and thereby, the infectiousness of HSV2. Clearly the HSV2 and HIV-1 epidemics parallel and enhance each other. Among populations with a high rate of HSV, the prevalence of HIV-1 would have been considerably lower if HSV infection had been prevented. Especially in African countries, the management of HSV2 is now considered to be a central issue to put on the ‘HIV-control’-agenda.

The herpes simplex viruses occur worldwide, although infection rates vary geographically and within populations. Infection with HSV1 occurs largely through non-sexual transmission early in life. Herpes simplex virus type 2 is usually transmitted sexually and is therefore considered to be a useful marker for sexual risk behaviour and for presence of HIV-1 in a population. The highest rate of HSV2 transmission occurs at age 15 to 40 years. In industrialized countries, homosexual men are a notably high risk group for infection.

MAPPING TRENDS AND TRANSMISSION: USE OF COHORT STUDIES

With the onset of the HIV epidemic, several cohort studies were set up to investigate HIV-1 and AIDS. These studies proved to be an invaluable tool in studying the natural history of disease, incidence and trends in incidence over time. In cohort studies, medical histories and behavioural questionnaires are taken and blood samples are drawn repeatedly and in a standardized fashion, yielding a broad spectrum of information. Such studies often have a large library of stored blood samples and not only provide prospective information but also open the way to gather retrospective information by screening these samples as new and important health issues arise. Investigators have thus gathered details on several cofactors of HIV-1 transmission and progression, such as HIV-1 RNA levels and genetic factors. For this thesis, samples were screened for antibodies against HHV8 and HSV.

Comparable behavioural data collected at intervals over calendar years allow for examining time trends and detecting their changes at an early phase. Moreover, prospective studies with multiple measurements have the optimal design to study disease incidence and time trends in incidence. When participants are initially uninfected with the disease under study, with repeated study visits, information can be obtained that precedes the disease onset. This feature of temporality allows cause to precede the effect in time, which is critical in studying cause-effect relationships such as the role of sexual techniques in virus transmission (a focus of thesis). Cohort studies can also serve as a starting point for other types of studies, such as case control or behavioural intervention studies, and even for clinical trials and vaccine studies.

When interpreting results from cohort studies, one has to bear in mind that incidence estimates can be biased due to the self-selection and continued participation of persons who are more likely to reduce their risk. One can never be sure whether cohort participants represent the ‘general’ at-risk population, although results from these prospective studies are perfectly valid for that segment having the same characteristics as the study population. Validation of
findings by comparing with another population (eg. visitors of an STD clinic) is recommended and described in this thesis.

A major concern for setting up and maintaining prospective follow up of a defined population over time is the cost and work involved. This aspect has to be counterbalanced by the amount and quality of information gathered and its utility for the public health system. Many cohorts set up to study HIV and AIDS, including the Amsterdam Cohort Studies, have proved their benefits in the past in various fields. They have the potential to continue to do so by monitoring risk behaviour and HIV, and with upcoming new HIV-1 related public health issues, such as the effect of HAART or HHV8, HSV interacting with HIV-1. Therefore, full advantage of available and forthcoming data should be taken and every effort should be made to continue follow-up of participants.

OUTLINE OF THIS THESIS

The studies undertaken for the present thesis are focused on the trends over time and/or modes of transmission of several pathogens as well as related trends in sexual behaviour. All studies used data from the Amsterdam Cohort Studies, with the exception of the third study of Chapter 1, which was performed using data from the Amsterdam sexually transmitted diseases (STD) clinic.

In Chapter 1, trends in sexual behaviour related to transmission of HIV-1 and other STD were studied using prospective data of homosexual men. We focused especially on the possible influence of HAART, since actual use of HAART or merely its availability has been speculated to be associated with a reduction of condom use. This topic was explored further by studying the impact of lipodystrophy, a relatively common side effect of HAART, on sexual behaviour and perceived health. A third study was conducted among homosexual visitors of the Amsterdam STD clinic to assess time trends in HIV-1 incidence. For this study, a newly described method was employed (STARHS or ‘detuned’ assay) to estimate HIV-1 incidence using data from cross-sectional HIV serosurveys.

In Chapter 2, three studies on HHV8 are presented. We studied its prevalence and incidence as well as its modes of transmission, using prospective data drawn from both homosexual men and drug users. Since knowledge about transmission routes could be important in terms of prevention activities, we examined whether specific sexual techniques were involved in the acquisition of HHV8 infection among homosexual men and whether HHV8 infection was linked with injection practices among drug users. In a final study, we attempted to define a clinical syndrome for primary HHV8 infection that may help clinicians to detect the infection in a patient.

In Chapter 3, time trends in the prevalence of HSV1 and HSV2 were studied among young homosexual men, using cross-sectional data. We also examined the effect of sociodemographic and sexual determinants on these trends.

Finally, in the general discussion, the main findings are interpreted in the light of updated literature. Their implications for current prevention programs are discussed, and recommendations for future research are presented.
REFERENCES


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