Epidemiological studies on STIs in heterosexuals and MSM

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CHAPTER 1

GENERAL INTRODUCTION
BACKGROUND

Sexually transmitted infections (STI) continue to be a serious health problem in the Netherlands.1 Certain ethnic minorities, young persons (<25 years of age) and MSM are important risk groups for STI.1,2 Chlamydia trachomatis (CT) infection is common in all three groups. Neisseria gonorrhoeae (NG) and syphilis are often found in MSM, and syphilis is more common in HIV-infected MSM than in HIV-negative MSM.1,2 Around 5% of MSM are infected with HIV,1,3 and since sexual risk behavior is high in this group, new epidemics such as hepatitis C and lymphogranuloma venereum (LGV) are first observed in HIV-infected MSM.4-7

Prevention and control of STI

Prevention and control of STI are important to reduce morbidity and mortality. For example, STI increases HIV transmission8-11 and HPV is associated with cervical12-16 and other cancers.17-19 In addition, treatment of STI prevents complications such as pelvic inflammatory disease20 and ectopic pregnancy.21

The prevention and control of STI is based on five major strategies described by the Centers for Disease Control and Prevention (CDC):22

- Education and counseling of persons at risk in order to achieve changes in sexual behaviors
- Identification of asymptptomatically infected persons and of symptomatic persons unlikely to seek diagnostic and treatment services
- Effective diagnosis and treatment of infected persons
- Evaluation, treatment, and counseling of sexual partners of persons who are infected with an STI
- Pre-exposure vaccination of persons at risk for vaccine-preventable STI.

Education and counseling of persons at risk in order to achieve changes in sexual behaviors

Knowledge about risk behaviors for STI is essential for targeting STI prevention programs to persons who are at risk and for optimisation of the prevention programs.
Known high-risk behaviors for STI include having multiple sexual partners and having sex without use of condoms. It has been shown that condom use can be increased by behavioural interventions, but unprotected sexual contact and inconsistent condom use are common. Chapter 2 analyses what characteristics of sexual partners and sexual partnerships influence condom use in heterosexuals.

The use of illicit and recreational drugs has been found to be associated with sexual risk behaviors and STI. However, these studies did not include large numbers of MSM. Chapter 3 describes the prevalence of STI in heterosexual and MSM participants of a biannual anonymous survey among STI clinic visitors and the association between drug use, sexual behavior and STI.

Identification of asymptomatically infected persons and of symptomatic persons unlikely to seek diagnostic and treatment services

In order to identify asymptomatically infected persons, STI screening programs have been developed. Examples of screening programs are: screening of pregnant women for syphilis, HIV and hepatitis B; and the Chlamydia Screening Implementation (CSI), which offered CT screening to 16 to 29 year-old residents in Amsterdam, Rotterdam and South Limburg. Another example is opportunistic hepatitis C screening among HIV-infected MSM who visit STI clinics.

Since STI are associated with HIV shedding and STI increase the susceptibility for acquisition of HIV infection, STI screening among HIV-infected patients may be important. Linkage of HIV treatment and STI screening could improve care for HIV-infected persons and diminish the risk of transmission of HIV to their sexual partners. In order to assess whether routine STI screening of asymptomatic HIV-infected MSM and heterosexuals in care at HIV clinics is needed in the Netherlands, two studies in chapter 4 examined STI prevalence and risk factors for STI in HIV-infected heterosexuals and HIV-infected MSM in care at 2 academic HIV clinics.
HIV-infected patients, especially those who are not treated with combination antiretroviral therapy (cART), have a decreased cellular immunity. Therefore, they might have an altered local inflammatory response and cytokine production after CT infection. Asymptomatic anal CT infections are common in HIV-infected MSM, however it is not known why anal CT in MSM is often asymptomatic. Chapter 5 analyses mucosal damage, inflammation and cytokine concentrations in the rectum of MSM, and analyses the influence of rectal CT infection, HIV infection and cART use.

**Effective diagnosis and treatment of infected persons**

Technological developments such as Nucleic Acid Amplification Tests (NAAT) and rapid HIV tests have improved diagnostic accuracy and speed and have decreased the time period between STI testing, diagnoses and treatment. When STI are diagnosed, effective treatment of infected persons is needed to decrease morbidity and to decrease STI transmission. However, effective treatment of STI, especially NG, is threatened by resistance against medication. In the Netherlands, the Gonococcal Resistance to Antimicrobials Surveillance programme (GRAS) was implemented to study the resistance of NG. This surveillance programme consists of systematically collected data on NG infections and resistance patterns linked with epidemiological data.

The introduction of the opting-out strategy in 2009, which means that all STI visitors are screened for HIV unless they actively refuse, has increased the number of STI visitors who are aware of their HIV status. This means that treatment can be started earlier and further transmission of HIV might be decreased. Nevertheless, it is estimated through modelling that around 40% of HIV-infected individuals in the Netherlands are unaware of their HIV-infection.

Another new epidemic is hepatitis C among HIV-infected MSM. The main expansion of the hepatitis C epidemic started after 2002, and it has been suggested that earlier identification of this epidemic could have limited its further spread through raising awareness of the risk of sexually acquired HCV among MSM.
Evaluation, treatment, and counseling of sexual partners of persons who are infected with an STI

Evaluation, treatment and counseling of sexual partners of persons who are infected with an STI disrupts transmission networks and reduces the risk of re-infection.\textsuperscript{76,77} Although the effect of partner notification has not been studied in the Netherlands,\textsuperscript{78} clinical care providers encourage persons who are infected with STI to notify their sexual partners and urge them to seek medical evaluation and treatment. The partner notification can be performed by the index patients themselves, or by the clinical care giver or by other means, for example by sending an anonymous note\textsuperscript{2} or by using social network approaches. Studies in populations where traditional contact tracing was difficult, for example populations of drug users or sex workers, showed that a social network approach increased case-finding and identified core groups involved in the transmission of STI in the USA.\textsuperscript{79,80} Also, internet-based partner notification is used, especially in MSM or when no other means of identification is possible due to the anonymous nature of the contacts.\textsuperscript{81} Although studies showed that patient-delivered partner therapy, in which partners of infected persons are treated without previous medical evaluation or prevention counseling, led to an increased number of treated partners and a decrease in re-infection rate \textsuperscript{82,83} its use is controversial and not used in the Netherlands.

It has been shown that most new HIV infections in MSM in Amsterdam occur within steady relationships.\textsuperscript{84} Increased duration of relationships is associated with unsafe sexual contact in heterosexuals,\textsuperscript{6} and in new or casual relationships condoms are used more often.\textsuperscript{85} However, partnerships factors associated with condom use are not well studied. In chapter 2 the influence of partnerships characteristics on condom use in heterosexual STI clinic visitors is analyzed.

Pre-exposure vaccination of persons at risk for vaccine-preventable STI

Vaccination can reduce susceptibility and ongoing transmission over a long period of time. Currently, effective hepatitis B and human papillomavirus (HPV) vaccines are available.\textsuperscript{86-89} Children born on or after 1 August 2011 are vaccinated against hepatitis B \textsuperscript{90} and free hepatitis B vaccination is offered to MSM and commercial sex workers.\textsuperscript{91}
HPV vaccination campaigns started in 2009 and are targeted at young girls. Two vaccines against HPV 16 and 18 have high, sustained efficacy against persistent type-specific infections and cervical lesions in women.\textsuperscript{88,89,92} One of these vaccines is quadrivalent, and protects also against HPV 6 and 11, which are causing genital warts.\textsuperscript{93} Current knowledge on prevalence of HPV is based mostly on the detection of HPV DNA on genital mucosa or skin. However, the majority of HPV infections are transient, and HPV DNA is detectable in cells from the cervix for less than a year.\textsuperscript{15,94} In contrast, HPV antibodies can persist for many years,\textsuperscript{95,96} and are thought to be a measure of lifetime exposure.\textsuperscript{97-101} Although not all HPV-infected persons develop an antibody response\textsuperscript{102} and the duration of the antibody response is not well defined, seroprevalence studies can be used to determine the current spread of HPV types in populations and to monitor the future effect of HPV vaccines.

HPV is associated with anal carcinoma and anal warts,\textsuperscript{103} particularly among HIV-infected MSM.\textsuperscript{104} Knowledge of seroprevalence of HPV in the general population and in MSM may aid in the discussion whether the existing girls-only vaccination programs should be broadened with vaccination of boys,\textsuperscript{105-107} or whether targeted vaccination of MSM should be initiated.\textsuperscript{108,109} Chapter 6 includes two studies on the seroprevalence of HPV types in the general population and in heterosexual and MSM STI clinic visitors.

**Study populations included in this thesis**

In this thesis we used three different settings to study the epidemiology of STI: the general population of Amsterdam, a large STI outpatient clinic in Amsterdam (heterosexuals and MSM) and two HIV outpatient clinics (heterosexuals and MSM).

In the Amsterdam Health Monitor 2004, a health monitoring survey in the general Amsterdam population, a random sample of residents aged 17 years or older was drawn from the Population Registry of Amsterdam, with over-sampling of people from Turkish and Moroccan origin.\textsuperscript{110} A standardised face-to-face interview concerning socio-demographics and relevant risk behaviour was conducted and serum samples of participants were tested for antibodies against 8 high-risk HPV types (chapter 6.1).
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The STI outpatient clinic of the Public Health Service of Amsterdam (GGD Amsterdam) offers free and anonymous STI testing and treatment. Roughly 20% of the attendees are MSM. Clients are routinely screened for NG, CT, syphilis, hepatitis B (if they are not known to already be infected or immune), and for HIV (unless they actively refuse). In addition, a long-standing bi-annual anonymous survey among STI clinic clients, originally started to monitor HIV prevalence, is conducted at the STI outpatient clinic. In waves, consecutive new attendees of the clinic are asked to participate, until approximately 1,000 attendees are included in a wave. The STI outpatient clinic was the setting of the studies reported in chapters 2, 3, 5, 6 and 7.2.

In the HIV outpatient clinic of the Academic Medical Centre in Amsterdam, the prevalence of and risk factors for STI in HIV-infected heterosexuals and HIV-infected MSM were studied (chapter 4). The study in HIV+ MSM was done in collaboration with the HIV-outpatient clinic of Erasmus Medical Centre in Rotterdam.

The research in this thesis has been conducted as part of the Infectious Diseases Network of the Academic Collaboration (“Academische Werkplaats”), the collaboration between the Academic Medical Centre in Amsterdam and the Public Health Service Amsterdam. The aim of this network is to connect research with practice as well as policy and to contribute to more evidence-based service practices in prevention and control programmes for infectious diseases. It tries to reach these goals by studying new and re-emerging infectious diseases in the public health field and communicating the results of these studies to other public health professionals, clinical-care providers and students, using a scientific approach to answer questions from the public health care.
OUTLINE OF THIS THESIS

Chapter 2 studies which characteristics of sexual partners or sexual partnerships influence condom use in heterosexuals.

Chapter 3 describes the prevalence of STI in participants of the biannual anonymous survey among STI clinic visitors and assesses the association between drug use, sexual behavior and STI in heterosexual and MSM participants.

Chapter 4 describes asymptomatic STI prevalence and assesses risk factors for STI in HIV-infected heterosexuals and MSM.

The study in chapter 5 examines the influence of rectal CT infection, HIV infection and cART use on rectal mucosal damage, inflammation and cytokine concentrations in MSM, possibly explaining the high prevalence of asymptomatic STI in HIV-infected MSM described in chapter 2.

Chapter 6 reports seroprevalence of and risk factors for high-risk HPV types in the general population of Amsterdam and in heterosexual and MSM STI clinic visitors.

In the general discussion in chapter 7, main findings are discussed and related to recent literature. Their implications for prevention and policy are discussed and recommendations for future research are presented.
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