Epidemiological studies on STIs in heterosexuals and MSM

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CHAPTER 7

GENERAL DISCUSSION
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The quality of current and future sexually transmitted infections (STI) prevention programs can be improved by providing new information about risk factors for STI and prevalence of STI. The studies described in this thesis assessed STI prevalence and STI risk factors in the general population, a large STI clinic and two HIV outpatient clinics. In addition, it was studied which characteristics of sexual partners or sexual partnerships influence condom use and whether sex-related drug use is associated with STI. Finally, the influence of *Chlamydia trachomatis* (CT) infection on rectal mucosal damage, inflammation and cytokine concentrations was studied.

In the Introduction of this thesis the five major prevention and control strategies proposed by Centers for Disease Control and Prevention (CDC) were described. Below we report how each study reported in this thesis contributes to each of these five strategies.

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

Many studies have analysed sexual risk behaviours in the past. However, when studying risk behaviour, partnership characteristics (e.g. duration of partnership, overlapping partnerships and age or ethnicity differences) are often overlooked. Chapter 2 analysed what characteristics of sexual partners and sexual partnerships influence condom use in heterosexuals. We found that no or inconsistent condom use was more common in partnerships when partners had the same ethnicity or when the partner was younger. Also, with increasing duration of the relationship and increasing number of sexual acts, consistent condom use was less common. On the other hand, having multiple sexual relationships at the same time was associated with consistent condom use. These results show that condom use also depends on partnerships characteristics.

Increased understanding of determinants associated with inconsistent condom use can contribute to more focussed STI prevention programmes aimed at increasing the use of condoms, for example by underlining the importance of using condoms with casual partners, and the importance of using condoms with a new steady partner for at least 3 months and testing of the person and their steady partner for STI before they stop using condoms. Based on the results of this study in heterosexual men and
women, it is recommended to include partnerships characteristics when studying determinants associated with condom use.

Chapter 3 describes the prevalence of STI in heterosexual and men having sex with men (MSM) participants of a biannual anonymous survey among STI clinic visitors, and the associations between drug use, sexual behaviour and STI. We found that sex-related drug use was common in this population and was associated with STI in women and MSM. Other studies also found that use of illicit and recreational drugs was associated with sexual risk behaviors\textsuperscript{2-12} and STI.\textsuperscript{13-23} However, these studies did not include large groups of MSM and did not study whether drug use was associated with STI after adjusting for sexual risk behaviour. We found that alkyl nitrites (poppers) use was very common among MSM and that poppers use was associated with STI, even after adjusting for sexual risk behaviour. This warrants further research into the effect of poppers on STI acquisition in MSM: do poppers have a direct biological effect on STI acquisition or does the altered mental state (as reported by Drumright et al)\textsuperscript{24} lead to increased number and duration of sexual acts, or to increased tissue damage? The question whether drugs lead to an increased number and increased duration of sexual acts could be studied by using an online study with MSM participants completing in daily diaries with information about their sexual activity and sex-related drug use that day. Since sex-related drug use is also common among swingers (heterosexual couples who have sex with other couples or singles) and swingers are a risk group for STI, the same study could be performed in swingers as well. In line with the results of chapter 2, partnerships characteristics should be studied in these proposed studies. The implication for prevention is that sex-related drug use should be addressed in STI prevention programmes, for example by informing the public that sex-related drug use may lead to high-risk sexual behavior and to STI.

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

Two studies in chapter 4 assessed STI prevalence and risk behaviour in asymptomatic HIV-infected heterosexuals and MSM visiting the HIV outpatient clinic for a regular consultation. In HIV-infected heterosexuals, sexual risk behaviour was not common
and STI prevalence was very low. In contrast, sexual risk behaviour was common in HIV-infected MSM and the prevalence of STI (chlamydia, gonorrhoea and syphilis) was high: 16%. This high prevalence could be the result of serosorting and not using condoms among HIV-infected MSM. In addition, 23% of HIV-infected MSM reported unsafe anal sex with HIV-negative partners in the last 6 months. Since STI are associated with HIV shedding and STI increase the susceptibility for acquisition of HIV infection, 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. Also, from a patient perspective, linkage of HIV treatment and STI care is beneficial. Currently, one of the barriers for the implementation of STI screening (other than syphilis screening) in MSM in HIV care is that is unknown whether this screening is cost-effective. The upcoming results of a current study into the cost-effectiveness of STI screening in MSM in HIV care will aid in this discussion.

Several participants of this study were diagnosed with a new hepatitis C infection. Incidence rates for 2011 suggest that there might be a real increase in hepatitis C infections in MSM in the Netherlands, which is not accounted for by increased testing rates. However, another study performed in HIV-infected MSM showed an increase in hepatitis C prevalence from 1995 to 2007 and an apparent levelling off in recent years. The new treatment options for hepatitis C seem promising and make hepatitis C screening among HIV-infected MSM even more important.

Asymptomatic rectal CT infections are common in HIV-infected MSM, however it is not known why rectal CT is often asymptomatic. Chapter 5 studied mucosal damage, inflammation and cytokine concentrations in the rectum of MSM, and analysed the influence of rectal CT infection, HIV infection and combination antiretroviral therapy (cART) use. We found that CT infection was associated with reduced concentrations of several cytokines in the rectum of HIV-negative MSM, but not of HIV-infected MSM. This was a surprising finding, since studies in persons with CT in urethra or cervix found that CT actually increased these cytokine concentrations. Neutrophilic inflammation and mucosal damage did not differ between HIV-infected MSM with or without CT, which is in line with the lack of symptoms in CT infected patients. The
exact process by which CT escapes from the immune mechanisms in the rectum, aimed at initiation of inflammation and eradication of a pathogen, needs to be clarified in further research.

**Effective diagnosis and treatment of infected persons**

Multiple anatomic site testing, whether based on risk behaviour or performed standard in certain risk groups, is not performed in all STI clinics in the Netherlands as a recent study showed.\(^{37}\) It is most likely that the same is true for STI screening in general practice. When patients have CT or NG at other sites than those sampled for testing, the chain of transmission is not broken. Several studies in these thesis showed the importance of multiple site testing: chapter 4 showed that among HIV-infected MSM only 14.7% of CT/NG infections would have been diagnosed when screening would be limited to urethral samples, and chapter 3 showed that 13.5% of female and 40% of MSM STI clinic visitors reported unsafe anal sex in the 6 months preceding the study visit and that anal CT and NG was common in those whore reported anal sex. Therefore, it is very important that general practitioners and STI clinics screen multiple anatomic sites in women and MSM when the patients report oral or anal sex after they are asked ‘Did you have had oral / anal sex in the past 6 months?’ Also, systematic screening of multiple anatomic sites in MSM, regardless of reported risk behaviour in the preceding months, should be evaluated. In addition, the percentage of anal CT in MSM that are LGV typed is currently 83% according to STI clinic information,\(^{34}\) but this should be 100% to improve treatment of LGV cases and stop the spread of LGV.

**Evaluation, treatment, and counselling of sexual partners of persons who are infected with an STI**

In several studies described in this thesis, the number of lifetime sexual partners and number of sexual partners in the preceding 6 months were studied. The range of number of sexual partners was wide and the number of sexual partners was higher in MSM (both lifetime sexual partners and sexual partners in the 6 months preceding the study visit). For example, in chapter 3 most heterosexual STI clinic visitors in Amsterdam reported between 0 and 2 casual sexual partners in the preceding
6 months, while most MSM STI clinic visitors reported between 2 and 15 casual partners. Since casual partners are sometimes anonymous partners, not all sexual partners of patients with an STI can be notified. The use of online dating sites as a place to meet sexual partners has increased in recent years. Sometimes, no other contact information than the profiles on these dating sites are available. It would be a promising development in partner counselling if it would be possible to send an STI warning message to the profiles of the sexual partners that could have been infected or could have infected the patient, and recently this has been made possible for one dating site (gay.nl).

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

Chapter 6 includes two studies on the seroprevalence of HPV types in the general population and in heterosexual and MSM STI clinic visitors. These studies showed that the seroprevalence of human papillomavirus (HPV) 16 and 18 were higher in those with receptive vaginal or anal intercourse. These findings can be explained by the theory posed by Kreimer and Stone that states that HPV infection in mucosal epithelium (e.g. of the vagina or anus) may be more likely to induce a humoral immune response than HPV infection at keratinised epithelium. This could result in more HPV seroconversion in groups with more exposure to mucosal epithelium. Support for this theory comes also from a study that found that the seroprevalence of HPV 6 and 16 was consistently higher in men with corresponding anal HPV infection compared to men with only genital infection.

HPV is associated with anal carcinoma and anal warts, which effects HIV-infected MSM in particular. The current HPV vaccination campaign is targeted at young girls, but in most countries where vaccination campaigns for girls have started, there is an ongoing debate whether boys should be vaccinated too. In Australia boys will be vaccinated from 2013 onwards, and in the USA HPV vaccination for boys is recommended. The assumed herd immunity that will protect boys from HPV infection by vaccinating girls will not protect MSM. Cost-effectiveness studies evaluated whether it would be cost-effective to vaccinate boys as well. However, only one of these studies took into account that a percentage of boys will have sex with men in their life. Since at the time no data on HPV 16 and HPV 18 seropositivity
in MSM (both HIV-negative and HIV-infected) were available, new cost-effectivity studies could benefit from the now provided data.

An effective hepatitis B vaccine is also available, and is offered to MSM and commercial sex workers, among others.\textsuperscript{46} However in chapter 4 we found that 14% of HIV-infected MSM were still at risk for hepatitis B since they were not successfully vaccinated. Given that sexual risk behaviour in this group was high and 1 out of 92 susceptible participants was diagnosed with an acute hepatitis B infection, studies that assess options to increase the effectiveness of hepatitis B vaccination in HIV-infected patients are important.

**CONCLUDING REMARKS**

This thesis underlines the importance of improvement of current prevention strategies for STI and the development of new prevention strategies, since risk behaviour and STI prevalence was common in nearly all studied populations and very common in HIV-infected MSM.

Linkage of HIV and STI care in MSM is very likely to be beneficial from a patient perspective and a public health perspective. For patients visiting the HIV clinic it means an easy, convenient STI screening possibility without waiting lines, extra appointments and possibly stigma concerning homosexuality, STI and HIV.

From a public health perspective, regular screening of HIV-infected MSM decreases transmission of both STI and HIV and gives insight in new epidemics such as LGV and hepatitis C. Not only because HIV-infected MSM have a high prevalence of asymptomatic STI which increases HIV shedding, but also because they have, in general, a high number of sexual partners, have high-risk sexual behaviour and report unsafe sex with HIV-negative men.
Rectal CT was the most common asymptomatic STI in HIV-infected MSM, which might be explained in part by our finding that CT seems to escape from the immune mechanisms in the rectum. It is likely that there is a reservoir of anal CT in MSM and women, since anal sex is commonly reported by MSM and women and CT is often asymptomatic. In addition, rectal CT is not diagnosed when only urethral or vaginal samples are taken for STI screening. STI clinics and general practitioners should therefore always consider testing at multiple anatomic locations, depending on risk behaviour or risk group.

In addition, in this thesis it is shown that the prevalence of vaccine hrHPV types was higher in those with receptive intercourse, both women with vaginal and/or anal sex and MSM who have receptive anal sex. Since HPV is associated with cervical and anal carcinoma and genital warts, of which anal carcinoma and anal warts affect HIV-infected MSM in particular, HPV vaccination cost-effectivity studies are only valid when they include in their model the percentage of boys who will in the future have sex with men, HPV seroprevalence rates among MSM and the prevalence of anal carcinoma and anal warts in MSM. And additionally, it should be considered whether vaccination of boys exclusively might be an option.

The risk of sex-related drug use should be added to current prevention programmes, and the influence of partner characteristics on condom use should also be used in these programmes.

Contact between research and practice should be supported and encouraged, since the use of research findings can increase evidence-based prevention and questions from practice may guide the research agenda. Studies that are relevant for practice will contribute to prevention strategies for STI in the Netherlands and eventually decrease the prevalence of STI and STI-related morbidity and mortality.
REFERENCES


