STDs and HIV infection

in men who have sex with men

Rotterdam cohort study

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bij mannen die seks hebben met mannen

Rotterdams cohort onderzoek

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chapter 1
general introduction

The research that comprises this thesis has been performed with data from the 'Rotterdam cohort study (ROHOCO)' which took place at the sexually transmitted diseases (STD) clinic of the department of Dermatology and Venereology of the Erasmus MC, University Medical Centre Rotterdam, The Netherlands.
Beginning in February of 1999, we recruited men who have sex with men (MSM) to participate in our cohort study. Homo- and bisexual STD clinic attendees were informed about the opportunity to take part in the study. In addition, men visiting gay bars and saunas in Rotterdam were asked to participate. Both HIV-positive and HIV-negative MSM could participate in this cohort study. To enrol a diverse group of men, trained volunteers visited so-called meeting places, where gay men have (anonymous) sexual encounters. Advertisements were published in newspapers and gay periodicals. The last participant was enrolled in February of 2000.
Cohort participants were tested for STDs and HIV every six months for a period of three years.

Data collection
Demographic and sexual behavioural data were collected during each semi-annual cohort visit. These included ethnic background, age, educational level, sexual orientation, number of sexual partners during the last six months, practice of anal intercourse, intravenous drug use, participation in prostitution and earlier diagnoses of STD including HIV infection. Additional (sex) behavioural data were collected with self-administered questionnaires.

Questionnaires
A total of three different (sex) behavioural questionnaires were used. During the first and fourth cohort visit all participants were asked to complete questionnaire number 1. Questionnaire number 2 had to be completed during the second and fifth cohort visits. Finally, the participants were invited to fill out questionnaire number 3 during the third and the last cohort visits.
All questionnaires had a standard page with questions on professional activities, salary, religious denomination, housing facilities, educational level, acculturation as well as sexual orientation, age of first (anal) sexual encounter, numbers of lifetime sexual partners and practice of anal intercourse with steady and/or casual partners.
Furthermore, questionnaire 1 had items on knowledge of transmission of STDs and HIV infection, perceived susceptibility to HIV infection and certain STDs (genital warts, genital herpes simplex infection, hepatitis A and hepatitis B infection), perceived severity of HIV infection and STDs and finally, questions on previous hepatitis A and B infections and hepatitis vaccination.

Questionnaire 2 had items on knowledge of transmission of STDs and HIV infection, perceived susceptibility to HIV infection and certain STDs (gonorrhoea, syphilis, chlamydial infection and hepatitis B infection), perceived severity of HIV infection and STDs and sex behavioural items concerning the relation with the steady partner. Finally this questionnaire also included items on undesirable sexual encounters.
Questionnaire 3 had items on knowledge of transmission of STDs and HIV infection, perceived severity of HIV infection and STDs and sex behavioural items concerning intercourse with casual partners. Finally it also included items on 'HIV-optimism', items on post exposure prophylaxis (PEP) and items on previous genital warts, its treatment and influence on sexual behaviour.

HIV-testing
Individual testing for HIV took place after counselling and written informed consent. Test results were personally given to the MSM involved. Those who did not want to know their serostatus were tested 'unlinked', in which case the blood sample was given a serial number which could not be linked to the individual. A leaflet, which was handed out to all participants, explained the procedure of HIV-testing beforehand.
The possibility of 'unlinked' HIV-testing was created for those who did not want to participate in the cohort study in case their HIV-serostatus had to be revealed.
New HIV cases were defined as positive test results in persons who either had never been tested before or tested negative previously.

Laboratory methods
All patients underwent a routine venereological examination using standardised procedures. Blood samples were taken to test for HIV-antibodies (micropartide enzyme immunoassay AxSym HIV-1/2 reagens; Abbott, Santa Clara, California, USA), syphilis (Treponema pallidum particle agglutination (TPPA)-test; Serodia-TPPA, Fujirebio Inc., Tokyo, Japan) and hepatitis B (anti-HBc and HBsAg, micropartide enzyme immunoassay IMX; Abbott, Santa Clara, Illinois, USA). The routine venereological examination also included testing for gonorrhoea (Gram-stained genital specimens for direct visualization of monomorphic Gram-negative diplococci within polymorphonuclear leukocytes; GC-Lect agarplates; Becton & Dickson Europe, Meylan, France), *Chlamydia trachomatis* infection (Cobas Amplicor PCR, Roche Diagnostic Systems; Branchburg USA) and microscopy of first-voided urine for non-specific urethritis (NSU). NSU was defined as the presence of > 6 leukocytes per 10^{-6} litre in the specimen of first-voided urine (KOVA-system; Hycor Biomedical Inc., Garden Grove, California, USA; in full accordance with the manufacturer's instructions) [1].
Gonorrhoea was diagnosed in case of Gram-negative diplococci within polymorphonuclear leukocytes or in the event of a positive culture. Patients with primary and secondary syphilis, and those with early latent syphilis, were categorised as having early syphilis. Early latent syphilis was diagnosed in patients without clinical signs, with a positive TPPA-test, a positive fluorescent treponemal antibody-absorption (FTA-abs) test and a positive Venereal Disease Research Laboratory (VDRL) test with a titre higher than or equal to 1:8. Subjects were asked

for a history of previous treatment for treponematoses, a negative syphilis serology in the past and a recent history of syphilitic symptoms, in order to guarantee a correct classification. Late latent syphilis was diagnosed in case of a positive TPPA-test, a positive FTA-abs test and a positive VDRL test with a titre below 1:8. Symptomatic as well as asymptomatic neurosyphilis was categorised as late syphilis [2]. Individuals with HBsAg, with or without HBeAg, were categorised as having infectious hepatitis B, whilst past hepatitis B infection was defined as the presence of anti-HBc without HbsAg.

Aim of the study

Although the association between HIV infection and sexual behaviour was investigated in numerous studies little is known on the association between STDs and behavioural determinants in MSM. Therefore, we started this three-year study on behavioural determinants of STDs and HIV infection in MSM aged 18 to 75 years.

In recent years, a large increase in gonorrhoea and early syphilis was reported in MSM in several cities such as San Francisco, London and Sydney [3-6]. Some studies even show signs of increasing HIV infection among MSM [7-9]. In the Netherlands, recent studies show increased early syphilis and rectal gonorrhoea in Amsterdam MSM [10].

Different explanations such as optimism due to HAART, 'AIDS-fatigue' (i.e. MSM accustomed to the risk of HIV infection after two decades of AIDS), increased sex seeking on internet and an increased opportunity for meeting sexual partners in saunas and backrooms were suggested for an increase in HIV infections [11-20].

When comparing STDs and HIV infections, it is necessary to realise that differences in risk perceptions between STD and HIV infections have been detected [21].

One of the aims of our study was to monitor the cumulative incidence of STDs and HIV infection in MSM and to investigate longitudinal behavioural changes during the three-year cohort study. In addition, increase in both HIV infection and STDs could be monitored together with behavioural determinants, which might be associated.

Apart from behavioural aspects, beliefs as well as determinants of health, knowledge of transmission of HIV and STDs, perceived severity of different STDs and HIV infection and perceived susceptibility to certain STDs and HIV infection could have an influence on the cumulative incidence of STDs and HIV infection.

Outline of this thesis

The studies undertaken in the present thesis were focused on the possible association between (cumulative) incidence of STDs and HIV infection and (sex) behavioural determinants. All studies used data from the Rotterdam cohort study. In chapter 3, we also used data from the Rotterdam STD clinic.

Chapter 1 is a general introduction. The aim of the study and the outline of this thesis are explained.

Chapter 2 summarises most important demographics, sex behavioural data as well as data on hepatitis A and B and genital warts of the Rotterdam cohort participants. Data were compared to findings of other national studies.

In chapter 3 the prevalence of STDs and HIV infections among attenders of the Erasmus MC STD clinic were studied during the years 1996 to 2000. Subgroup analyses of these 5 years were the basis of further analyses in MSM in this thesis.

In chapter 4 demographics, sexual behaviour and STDs and HIV prevalence were compared between two groups of MSM: one group consisted of STD clinic attenders and the second group were the participants of the Rotterdam cohort study. Reports as this are important in order to investigate whether MSM visiting the STD clinic at their own initiative, and those participating in a newly started cohort study were different with regard to demographics and sexual behaviour. Comparison of these different groups of MSM allows a more general assessment of behavioural indicators and possible risk factors for STD and HIV.

In chapter 5, the first study on human papillomavirus (HPV) infection and possible risk factors in participants of the Rotterdam cohort study is presented. To develop strategies for prevention and early treatment of HPV-associated high grade anal squamous intraepithelial lesions (HSIL) and anal cancers in predominantly HIV positive MSM, a better understanding of sex behavioural risk factors is needed.

In chapter 6, as a sequel of our first HPV study, research concerning acquisition and clearance of anal HPV infection in participants of the cohort study is presented. The difference in the incidence of anal cancers between HIV-positive and HIV-negative MSM may be explained by a different acquisition and clearance rate between those MSM.

In chapter 7 the cumulative incidence of STDs and HIV infection related to perceived HIV/AIDS threat since HAART and PEP availability was studied. This is, to our knowledge, the first study in which the relationship between the incidence of STDs and HIV infection, and HAART- and PEP-related beliefs in MSM has been investigated. In this study we focused on the incidence of STD and HIV diagnoses, rather than on self-reported unprotected anal intercourse. Longitudinal data that relate new STD and HIV infections to HAART and PEP-related perceptions contributes to our understanding of the - extensively debated - issue regarding the existence of any association between so-called 'HIV optimism' and risky sexual behaviour in HIV-negative MSM.

In chapter 8 the cumulative incidence of STDs and HIV infection was related to perceived severity, perceived susceptibility and knowledge of STD and HIV. In this study we examined both knowledge and beliefs, in order to find an association with low and high risk sexual behaviour in MSM.

In the general discussion (chapter 9), finally, the findings of this thesis are interpreted in the light of the recent literature. Their possible implications for current prevention programs are discussed, and recommendations for future research are presented.

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chapter 2

demographics, sex behavioural data and self-reported earlier STDs

Recruitment of the participants

Beginning in February of 1999, we recruited 286 MSM to participate in our Rotterdam cohort study. Homo- and bisexual visitors of the STD clinic were informed about the opportunity to take part in the study. In addition, men visiting gay bars and saunas in Rotterdam were asked to participate in the study. Both HIV-positive and HIV-negative MSM could participate in this cohort study. To enrol a diverse group of men, trained volunteers visited so-called meeting places, where gay men have (anonymous) sexual encounters. Advertisements were published in newspapers and gay periodicals. The last participant was enrolled in February of 2000.

residence	age < 40 years	age ≥ 40 years	total (%)
region			
Rotterdam	113	108	221 (77.3)
The Hague	10	14	24 (8.4)
Hook of Holland	11	8	19 (6.6)
Amsterdam	1	3	4 (1.4)
Leiden	1	-	1 (0.3)
Utrecht	2	1	3 (1.1)
Breda	1	7	8 (2.8)
Den Bosch	2	1	3 (1.1)
other	2	1	3 (1.1)
total	143	143	286 (100)

More than three-quarter of the participants lived in Rotterdam. A minority of these men (less than 5%) had symptoms when they came for their first planned, semi-annual visit. The majority of these men (189/286; 66.1%), had never visited the Rotterdam STD clinic before. Only 63/286 (22.0%) visited the STD clinic during the last two years before enrolment.

Sexual orientation and educational level

The majority of the participants (251/286; 87.7%) were homosexually orientated. In general, both homosexual and bisexual men had high education (106/251; 42.2% versus 16/35; 45.7%; $p = 0.87$). In homosexual men 123/251 (49.0%) of the men were older than 39 years of age, compared to 20/35 (57.1%) of the bisexual men ($p = 0.65$)

	age < 40 years			age ≥ 40 years			total
	educational level			educational level			
	low	middle	high	low	middle	high	
sexual orientation							
homosexual	12	63	53	15	54	54	251
bisexual	6	4	5	4	6	10	35
total	18	67	58	19	60	64	286

Educational level was defined as 'low' with school attendance up to the age of about 16 years, as 'middle' with school attendance up to the age of about 18 years, and as 'high' with a college degree or equivalent.

educational level		
low	37	12.9%
middle	127	44.3%
high	122	42.7%
total	286	100%

Age

The median age of all MSM at enrolment was 39.5 years (inter-quartile range, IQR, : 33 – 48 years). The youngest participant was 18 years and the oldest 75 years of age.

age distribution in clusters of five years		
15 – 19 years	1	0.3 %
20 – 24 years	12	4.2 %
25 – 29 years	24	8.4 %
30 – 34 years	55	19.2 %
35 – 39 years	51	17.8 %
40 – 44 years	50	17,5 %
45 – 49 years	33	11,5 %
50 - 54 years	34	11,9 %
> 55 years	26	9,1 %
total	286	100 %

Half of the participants were younger than 40 years of age. The median age was higher than that in the first and second national survey among MSM in the Netherlands (Monitor study 2000 and 2003 respectively), comparable to some of the early Amsterdam cohort studies, but higher than later studies done in the Amsterdam cohort [1-4].

Living accommodation

More than half of the participants lived alone (169/286, 58.7%). One in three lived with his steady partner (92/286, 32.5%). Five percent lived with 'others' (e.g. in a communion) and 3.5% lived with his parent(s) or supporter(s).

living accommodation		
alone	169	58.7 %
living with steady partner	92	32.5 %
living with others (communion, apartments)	15	5.2 %
living with parent(s) or supporter(s)	10	3.5 %
total	286	100 %

Religious denomination

Of all participants 112/286 (39.2%) had a religious denomination. Most MSM were Protestant (42.9%) or Catholic (42.0%), two main religions in the Netherlands.

religious denomination		
Protestant	48	42.9 %
Catholic	47	42.0 %
Islamite	3	2.7 %
Jewish	2	1.8 %
Hindu	1	0.9 %
Buddhist	1	0.9 %
other	10	8.9 %
total	112	100 %

Nationality

Most participants were of native Dutch descent (272/286, 95.1%). Other nationalities were British, Antillean, Surinamese, Singaporean, Turkish, Moroccan, Belgian, Italian and Indonesian.

ethnicity		
native Dutch	272	95.1 %
British	3	1.0 %
Antillean	2	0.7 %
Surinamese	2	0.7 %
Singaporean	2	0.7 %
Turkish	1	0.3 %
Moroccan	1	0.3 %
Belgian	1	0.3 %
Italian	1	0.3 %
Indonesian	1	0.3 %
total	286	100 %

'Self-identified' sexual identity

Of all MSM 217/285 (76.1%) identified themselves as 'exclusively homosexual'. Those who had sex with both men and women during the preceding 6 months more often identified themselves as 'almost exclusively homosexual' (10/35, 28.6%) or 'equally homosexual and heterosexual' (10/35, 28.6%).

'self-identified' sexual identity			
	sexual behaviour		
	homosexual	bisexual	total (%)
exclusively homosexual	217	0	217 (76.1)
almost exclusively homosexual	20	10	30 (10.5)
predominantly homosexual	8	9	17 (6.0)
equally homosexual and heterosexual	4	10	14 (4.9)
predominantly heterosexual	0	3	3 (1.1)
almost exclusively heterosexual	0	3	3 (1.1)
exclusively heterosexual	1	0	1 (0.4)
total	250	35	285

Steady and casual partners

Of all MSM 21/263 (12.2%) stated at their second cohort visit to have had only sex with one steady partner during the last six months. Both homosexually and bisexually orientated men equally often only had sexual intercourse with one steady partner ($p = 1.00$). Of the homosexual men 94/233 (40.3%) only had sex with casual partners during the last six months, compared to 14/30 (46.7%) of bisexual men ($p = 0.72$).

A total of 87% of all participants stated to have sexual contacts with casual partners. In the national survey among MSM in the Netherlands of 2000 and 2003, these percentages were 73 and 70% respectively ($p = 0.079$ and $p = 0.033$) [1,2].

Both having sex with one steady partner only and having sex with casual partners only were as often reported below and over the age of 40 years ($p = 0.36$ and $p = 0.73$ respectively).

sexual contacts with steady and casual male partners			
	sexual behaviour		
	homosexual	bisexual	total (%)
no partners	2 (0.9)	0	2 (0.8)
only steady partner	29 (12.4)	3 (10.0)	32 (12.2)
only casual partners	94 (40.3)	14 (46.7)	108 (41.1)
both steady and casual partners	108 (46.4)	13 (43.3)	121 (46.9)
total	233 (100)	30 (100)	263 (100)

sexual contacts with steady and casual male partners			
	age		
	< 40 years	≥ 40 years	total (%)
no partners	1 (0.8)	1 (0.8)	2 (0.8)
only steady partner	13 (10.0)	19 (14.3)	32 (12.2)
only casual partners	56 (43.1)	52 (39.1)	108 (41.1)
both steady and casual partners	60 (46.2)	61 (45.9)	121 (46.9)
total	130 (100)	133 (100)	263 (100)

With regard to educational level no difference were seen in steady or casual partnerships.

sexual contacts with steady and casual male partners				
	educational level			
	low (%)	middle (%)	high (%)	total (%)
no partners	0	1 (0.8)	1 (0.9)	2 (0.8)
only steady partner	4 (13.3)	15 (12.3)	13 (11.7)	32 (12.2)
only casual partners	15 (50.0)	47 (38.5)	46 (41.4)	108 (41.1)
both steady and casual partners	11 (36.7)	59 (48.4)	51 (45.9)	121 (46.9)
total	30 (100)	122 (100)	111 (100)	263 (100)

Estimated number of lifetime sex partners

The median number of estimated lifetime sex partners was 100 (IQR: 30 - 300). One third (88/277, 31.8%) estimated their number of lifetime partners between 11 and 50. In MSM younger than 40 years of age the median number was 50 (IQR: 20 - 150) compared to a median number of 150 (IQR: 50 - 600) in the older MSM. MSM who exclusively had homosexual contacts, had a median estimated number of lifetime partners of 100 (IQR: 30 - 356). Bisexual men had a median estimated number of lifetime partners of 50 (IQR: 15 - 200).

estimated number of lifetime sex partners		
1	1	0.4 %
2 - 5	12	4.3 %
6 - 10	10	3.6 %
11 - 50	88	31.8 %
51 - 100	48	17.3 %
101 - 500	69	24.9 %
> 500	49	17.7 %
	277	100 %

First sexual intercourse with a male partner

The median age of the first sexual intercourse with a male partners was 18 years (IQR: 15 – 23). Of the homosexual men 154/246 (62.6%) had had there first sexual intercourse with a male partner before the age of twenty years compared to 13/35 (37.1%) of the bisexual men (p = 0.16).

age of first sexual intercourse with a male partner			
	sexual orientation		
	homosexual (%)	bisexual (%)	total (%)
< 20 years	154 (62.6)	13 (37.1)	167 (59.4)
≥ 20 years	92 (37.4)	22 (62.9)	114 (40.6)
total	246 (100)	35 (100)	281 (100)

MSM with a lower education have their first sexual intercourse with a male partner at an earlier age (median age = 17 years), compared to higher educated MSM (median age = 19.5 years). Twenty-five of 35 (71.4%) lower educated MSM had sex with a male partner before the age of 20, compared to 59 of 118 (50.0%) higher educated MSM (p = 0.28).

age of first sexual intercourse with a male partner				
	educational level			
	low (%)	middle (%)	high (%)	total (%)
< 20 years	25 (71.4)	83 (64.8)	59 (50.0)	167 (59.4)
≥ 20 years	10 (28.6)	45 (35.2)	59 (50.0)	114 (40.6)
total	35 (100)	128 (100)	118 (100)	281 (100)

First anal sexual intercourse with a male partner

At the first cohort visit 259 of 284 (91.2%) of the participants stated to ever have had anal sexual intercourse. The median age of these MSM at their first anal sexual intercourse was 23 years (IQR: 19 - 29). Generally, homosexual men had their first anal sexual intercourse at an earlier age (median age 22 years, IQR: 19 - 28) than bisexual men (median age 29 years, IQR: 21 - 35).

age of first anal sexual intercourse with a male partner			
	sexual orientation		
	homosexual (%)	bisexual (%)	total (%)
< 20 years	66 (28.6)	2 (8.7)	68 (26.8)
≥ 20 years	165 (71.4)	21 (91.3)	186 (73.2)
total	231 (100)	23 (100)	254 (100)

MSM with a lower education appeared to have their first anal sexual intercourse with a male partner at an earlier age (median age = 21 years) than higher educated MSM (median age = 24 years). Eight of 28 (28.6%) lower educated MSM had anal sex with a male partner before the age of 20, compared to 21 of 113 (18.6%) higher educated MSM (p = 0.45).

age of first anal sexual intercourse with a male partner				
	educational level			
	low (%)	middle (%)	high (%)	total (%)
< 20 years	8 (28.6)	39 (34.5)	21 (18.6)	68 (26.8)
≥ 20 years	20 (71.4)	74 (65.5)	92 (81.4)	186 (73.2)
total	28 (100)	113 (100)	113 (100)	254 (100)

Anal sex

This Table summarises anal sexual intercourse with a male partner reported at the six cohort visits. The number of MSM who stated never to have had anal sex drops from the first cohort visit to the last visit. Anal sex had been practised during the preceding six months in 64.0, 66.3, 68.2, 63.8, 66.7 and 68.4% of the participants. According to the results of the national survey among MSM in 2003, since the year 2000 there is an increase in anal sexual intercourse in MSM in the Netherlands [2]. The percentage of unprotected anal sex did not change in this study.

anal sexual intercourse with a male partner							
	cohort visit	1	2	3	4	5	6
never		20.3%	17.2%	15.3%	10.4%	13.9%	10.7%
previous six months	- IAS & RAS	36.4%	34.5%	40.1%	32.2%	35.2%	38.3%
	- only IAS	15.4%	17.6%	15.7%	15.8%	17.6%	13.1%
	- only RAS	12.2%	14.2%	12.4%	15.8%	13.9%	17.0%
ever		15.7%	16.5%	16.5%	25.8%	19.4%	20.9%
total (N)		286	261	242	240	216	206

IAS: insertive anal sex; RAS: receptive anal sex

Condom use during anal sexual intercourse

All participants who ever had anal sexual intercourse were asked at the first and at fourth cohort visit whether they had ever used condoms during anal intercourse. During the first cohort visit a percentage of 13.4% stated to 'never' or 'seldom' use condoms. This percentage decreased almost with 50% at the fourth visit: only 7.0% stated to 'never' or 'seldom' use condoms in anal sex.

In MSM with a steady partner more than 40% never used condoms during receptive and insertive anal sex. Less than one in three always used condoms. Comparing the first and fourth cohort visit, more MSM stated to 'always' use condoms at the latter (15.7 versus 20.9%).

condom use during anal sexual intercourse		
	cohort visit 1	cohort visit 4
never	7.1%	2.8%
seldom	6.3%	4.2%
sometimes	11.8%	10.3%
most times	49.0%	51.6%
always	25.9%	31.0%
	100%	100%

condom use during receptive anal sexual intercourse with steady partner		
	cohort visit 1	cohort visit 4
never	46.4%	38.1%
seldom	11.6%	14.3%
sometimes	5.8%	11.1%
most times	5.8%	9.5%
always	30.4%	27.0%
	100%	100%

condom use during insertive anal sexual intercourse with steady partner		
	cohort visit 1	cohort visit 4
never	47.1%	42.4%
seldom	17.6%	6.1%
sometimes	7.4%	9.1%
most times	5.9%	15.2%
always	22.1%	27.3%
	100%	100%

Negotiated safety

Slightly more than 40% of participants agreed with his steady partner to only have protected anal sexual intercourse with casual partners. More than 20% had no agreements at all. Another 20% agreed to have no sexual intercourse at all with casual partners. The national survey among MSM (Monitor study) concluded in 2003 that 8% of those who agreed to be monogamous did not commit to this agreement. Of those who did agree not to have anal

intercourse, or not to have unprotected anal intercourse, more than 20% did not commit to their negotiated safety agreement [2].

negotiated safety regarding sexual intercourse with steady and casual partner(s)		
	cohort visit 1	cohort visit 4
no agreements	22.9%	21.5%
monogamous; no sex with casual partners	20.1%	23.1%
no anal intercourse with casual partners	14.6%	12.3%
only protected anal intercourse with casual partners	41.7%	42.3%
both protected and unprotected anal intercourse	0.7%	0.8%
	100%	100%

HIV-testing

During the first cohort visit 109 of the 186 (38.1%) MSM appeared to have never been tested for HIV. During the six cohort visits all MSM were tested on HIV. Test results were personally given to the patients involved. Those who did not want to know their serostatus were tested 'unlinked', in which case the blood sample was given a serial number that could not be linked to a certain individual.

During the six cohort visits an increasing number of MSM wanted to been tested individually for HIV.

HIV-testing during cohort visits						
cohort visit	1	2	3	4	5	6
individual HIV test	75.7%	80.4%	83.8%	83.4%	81.4%	86.7%
unlinked HIV test	24.3%	19.6%	16.2%	16.6%	18.6%	13.3%

Reason for 'unlinked' HIV-testing

The reason most often given for 'unlinked' HIV testing, rather than individual HIV testing was being afraid of distressing results. At the six visit more participants said to have had no risky sexual intercourse as argument to prefer 'unlinked' HIV testing, compared to the first visit.

reasons for 'unlinked' HIV-testing during cohort visits						
cohort visit	1	2	3	4	5	6
no risky sexual behaviour	27.8%	38.5%	24.1%	29.4%	44.1%	47.1%
afraid of distressing result	72.2%	61.5%	75.9%	70.6%	55.9%	51.9%

Hepatitis A

Viral hepatitis is not uncommon among MSM. Hepatitis A is less common than hepatitis B and can be sexually transmitted by 'rimming' (oro-anal sexual contact). Participants were not routinely tested for hepatitis A during the cohort study. More Western European citizens travel throughout the world to visit exotic places which increases the rate of hepatitis A infection not caused by the sexual route. More than 50% of those who stated to have had hepatitis A in the past associated this with sexual intercourse. A minority related their infection with 'eating food' in endemic countries (up to 15%) or with holiday in general (up to 10%). More MSM had themselves vaccinated for hepatitis A during the cohort study.

hepatitis A		
	cohort visit 1	cohort visit 4
never had hepatitis A	84.5%	70.8%
had hepatitis, not sure whether it was hepatitis A	4.3%	4.7%
vaccinated against hepatitis A	4.0%	19.5%
ever had hepatitis A	7.2%	5.1%
	100%	100%

Hepatitis B

In MSM hepatitis B is more common than hepatitis A. All participants were routinely tested for hepatitis B during all cohort visits. Only those who had a positive anti-HBc and a negative HBsAg were considered as hepatitis B immune. Those who had a positive HBsAg for a period longer than 6 months were considered carriers. At the first cohort visit 74/286 (25.9%) MSM were hepatitis B immune. Only 37 of these 74 (50.0%) participants were aware of this immunity. A majority of 22/37 (59.5%) MSM associated their hepatitis immunity with sexual transmission. All three carriers were aware of their infectious hepatitis. Two of these MSM (66.7%) associated this infectious hepatitis B with sex. All uninfected participants were advised to undergo a vaccination for hepatitis A and B at the local department of Infectious Disease Control of the Municipal Health Service.

hepatitis B		
	cohort visit 1	cohort visit 4
never had hepatitis B	79.2%	50.4%
had hepatitis, not sure whether it was hepatitis B	3.9%	7.1%
vaccinated against hepatitis B	6.4%	24.8%
ever had hepatitis B	10.6%	17.3%
	100%	100%

STDs in the past

Of all participants 123/286 (43.0%) stated to have never had an STD in the past. The most often reported STD was gonorrhoea.

former STDs	cohort visit 1
gonorrhoea	76 (26.6%)
condylomata acuminata (genital warts)	49 (17.1%)
non-specific urethritis (NSU)	42 (14.7%)
Chlamydia trachomatis infection	40 (14.0%)
hepatitis B	37 (12.9%)
syphilis	30 10.5%)
genital herpes simplex virus infection	13 (4.5%)
unknown STD	13 (4.5%)
trichomoniasis	1 (0.3%)

Condylomata acuminata (genitals warts)

Genital warts or condylomata acuminata are very common among MSM. In this cohort study 63/243 (25.9%) stated to have or have had genital warts. Most often warts were located around the anus or in the rectum.

location of genital warts	questionnaire at cohort visit 3
perianal	65.1%
rectum	22.2%
penile shaft	19.0%
glans penis	14.3%
urethral meatus	4.8%
groin	4.8%
mouth	4.8%
scrotum	3.2%
other	-

Genital warts disappeared after a median period of 3 months (IQR: 1 – 10 months). This period ranged from 1 to 72 months. According to 36 of 62 (58.1%) MSM with genital warts (in the past), this STD had influence on their sex life. Of these men, 71% was anxious to infect sexual partners and 70% stated to avoid certain sexual techniques.

influence on sex life due to genital warts (mean scores) 1 = does strongly disagree; 2 = does disagree; 3 = does agree; 4 = does strongly agree	questionnaire at cohort visit 3
avoids certain sexual techniques	2.9
anxious to infect sexual partner	2.8
considered himself as 'dirty'	2.1
sexual intercourse with fewer partners	2.0
less often sexual intercourse	2.0
never thinks about genital warts during sex	1.2

Most MSM had been treated for their genital warts. The most often mentioned treatment was cryotherapy. Forty of the 63 (63.5%) MSM with genital warts (in the past) were treated with liquid nitrogen. Almost 60% of all MSM stated to have been treated with two or more treatment modalities. Five percent had ever used four different therapies before their genital warts were cured.

therapy of genital warts	questionnaire at cohort visit 3
cryotherapy	63.5%
podofyllin at the hospital	46.0%
podofyllotoxin self application	27.0%
electro cauterisation	17.5%
surgical removal	9.5%
other	6.3%
none	1.6%

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demographics and sex behavioural data

chapter 3

Prevalence of STD and HIV infections among attenders of the Erasmus MC STD clinic, Rotterdam, the Netherlands, during the years 1996 to 2000

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Abstract

The purpose of the study was to investigate possible changes in the prevalence of STD and HIV collected at a Dutch STD clinic in the period 1996 to 2000.
Age, gender, ethnic background, sexual orientation, intravenous drug use and STD or HIV infection in persons attending an STD outpatient clinic were analysed and compared.
The prevalence of HIV infection among the clinic visitors remained rather stable. The prevalence of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections increased significantly among heterosexual men and heterosexual women. Among homo- and bisexual men a significant increase was seen in chlamydial infections only.
Because of the increasing prevalence of gonococcal and chlamydial infections among STD clinic visitors in Rotterdam, more attention should be paid to coordinated preventive activities, such as health education and contact tracing. Further subgroup analyses should be done in order to get more information on risk behaviour in the different groups.

Introduction

At the Erasmus MC Sexually Transmitted Diseases clinic data related to socio-demographic background, sexual behaviour and present or past STD are collected since 1993.[1] Data are recorded in order to detect changes in the epidemiology of STD.
A recent study from Amsterdam showed a substantial rise in rectal gonorrhoea and early syphilis among homo- and bisexual men and a less dramatic increase of gonorrhoea and syphilis among heterosexual men and women.[2] Studies in the United States, the United Kingdom and other western European countries showed similar trends among homo- and bisexual men.[3-6]
To investigate whether the trends observed in Amsterdam were also present in Rotterdam, STD and HIV diagnoses over a five-year period were analysed. Attention was paid in particular to possible changes in the prevalence rate of gonococcal and chlamydial infection, early syphilis, non-specific urethritis (NSU) and HIV infection among homo- and bisexual men, in comparison to heterosexual men and women.

Methods
Study Population
Data from 1996 through 2000 concerned all new clinic visits. New visits were defined as patients visiting the Rotterdam clinic for the first time or as those already known but seeking care for a new problem. As a routine, all patients were interviewed by a physician who collected information about e.g. ethnic background, gender, age, sexual orientation, intravenous drug use, participation in prostitution and earlier diagnoses of STD and HIV infection.
All patients were allocated to one of the following groups: heterosexual women, homo- and bisexual women, heterosexual men, homo- and bisexual men and intravenous drug users. When information concerning intravenous drug use or sexual orientation was missing, patients were classified as 'unknown'.
Patients who had had sexual contact with at least one person of the same sex during the last six months were registered as homosexual. When sexual contact with a person from the opposite sex had taken place as well, they were characterised as bisexual.
Persons who declared use of intravenous drugs after 1980 were registered as intravenous drug users, regardless of sexual orientation. For HIV analyses all women were classified into one group because of the small number of homo- and bisexual women.

HIV-testing
Individual testing on HIV took place after counselling and written informed consent. Test results were personally given to the patients involved. Patients who did not want to know their serostatus were tested 'anonymously', in which case the blood sample was given a serial number which could not be linked to a certain individual, unless patients refused ('opting out'). This anonymous testing is being done as part of an HIV sentinel surveillance program in the Netherlands. A leaflet handed out to all new patients explained the procedure of HIV testing

beforehand.
New HIV cases were defined as positive test results in persons who either had never been tested before or tested negative previously. Exceptions to this routine testing were only made when a patient refused to have a blood sample taken or wanted to be tested selectively, e.g. for chlamydia only.

Laboratory methods
All patients underwent a routine venereological examination, using standardised procedures. Blood samples were taken for a test on HIV-antibodies (before July 1997: enzyme linked fluorescent assay Vidas AxSym HIV reagens; Biomerieux, Lyon, France and after July 1997: micropartide enzyme immunoassay AxSym HIV-1/2 reagens; Abbott, Santa Clara, California, USA), syphilis (*Treponema pallidum* particle agglutination (TPPA)-test; Serodia-TPPA, Fujirebio Inc., Tokyo, Japan) and hepatitis B (anti-HBc and HBsAg, before July 1997 by micropartide enzyme immunoassay AxSym reagens; Abbott, Santa Clara, California, USA and after July 1997: micropartide enzyme immunoassay IMX; Abbott, Santa Clara, Illinois, USA). The routine venereological examination also included testing on gonorrhoea (Gram-stained genital specimens for direct visualisation of monomorphic Gram-negative diplococci within polymorphonuclear leucocytes (PMNL); GC-Lect agarplates; Becton & Dickson Europe, Meylan, France), *Chlamydia trachomatis* infections (before January 1997: Gen-Probe (PACE 2 assay), Gen-Probe Inc., San Diego, California, USA; from January 1997 onwards: Cobas Amplicor PCR, Roche Diagnostic Systems; Branchburg USA) and microscopy of first-voided urine for non-specific urethritis (NSU), in men only. NSU was defined as the presence of > 6 leucocytes per 10^{-6} litre of specimen of first-voided urine (KOVA-system; Hycor Biomedical Inc., Garden Grove, California, USA; in full accordance with the manufacturer's instructions).[7] Gonorrhoea was diagnosed in case of Gram-negative diplococci within PMNL or in case of a positive culture. Early latent syphilis was diagnosed in case of a positive TPPA-test, a positive fluorescent treponemal antibody-absorption (FTA-ABS) test and a positive Veneral Disease Research Laboratory (VDRL) test with a titre greater than or equal to 1:8. Patients with primary and secondary syphilis were also categorised as early syphilis.

Patient investigation
Tests for rectal infections with gonorrhoea and chlamydia in men were done when receptive anal sex had taken place, or in case of complaints of the rectum. In women rectal tests only took place in case of complaints of the rectum. Oropharyngeal tests for gonorrhoea were done in all men having sex with men.

Statistical Methods
Data were compared in order to assess statistically significant differences in the prevalence of STD and the number of new HIV cases among the subgroups defined above. Prevalence was calculated as the number of positive tests per 100 tested individuals. For testing time trends of percentages the chi-square trend test was used. For testing time trends of absolute numbers (e.g., the number of clinic visits) regression analysis was used.

Table 1. Gender and sexual orientation of all tested patients in 1996 - 2000; the presented figures are numbers and (percentages).

year	1996	1997	1998	1999	2000	totals
men	(n = 1792) number (%)	(n = 2048) number (%)	(n = 1879) number (%)	(n = 1924) number (%)	(n = 1961) number (%)	(n = 9604) number (%)
heterosexual	1480 (85.6)	1488 (72.7)	1499 (79.8)	1539 (80.0)	1563 (79.7)	7569 (78.8)
homosexual	206 (11.5)	226 (11.0)	227 (12.1)	254 (13.2)	262 (13.4)	1175 (12.2)
bisexual	50 (2.8)	45 (2.2)	80 (4.3)	55 (2.9)	80 (4.1)	310 (3.2)
iv-drug use	42 (2.3)	265 (12.9)	48 (2.6)	20 (1.0)	20 (1.0)	395 (4.1)
unknown	14 (0.8)	24 (1.2)	25 (1.3)	56 (2.9)	36 (1.8)	155 (1.6)
women	(n = 1518) number (%)	(n = 2194) number (%)	(n = 1820) number (%)	(n = 1887) number (%)	(n = 1977) number (%)	(n = 9396) number (%)
heterosexual	1439 (94.8)	1747 (79.6)	1657 (91.0)	1692 (89.7)	1804 (91.2)	8339 (88.8)
homosexual	1 (0.1)	13 (0.6)	6 (0.3)	6 (0.3)	12 (0.6)	40 (0.4)
bisexual	28 (1.8)	18 (0.8)	25 (1.4)	55 (2.9)	44 (2.2)	170 (1.8)
iv-drug use	42 (2.8)	382 (17.4)	110 (6.0)	97 (5.1)	71 (3.6)	702 (7.5)
unknown	8 (0.5)	34 1.5)	22 (1.2)	37 (2.0)	46 (2.3)	147 (1.6)
	(n = 3310)	(n = 4242)	(n = 3699)	(n = 3811)	(n = 3938)	(n = 19000)

Results

Characteristics of the population

In the period 1996 - 2000 a total of 19,000 patients visited the Rotterdam STD clinic. The annual number of patients increased from 3310 in 1996 to 3938 in 2000 ($p = 0.525$). The largest increase was seen among heterosexual women ($p = 0.132$). Table 1 summarises gender, and sexual orientation of all tested patients. The percentage of homosexual men among all male patients increased over the years ($p = 0.006$). In the year 2000, 342 out of 1961 male patients (17.5%) were homo- or bisexual and 56 out of 1977 female patients (2.8%).

There were no statistically significant changes in the ethnicity of the visitors over the years. In the year 2000, more than two-thirds (66.5%) of the patients were of Dutch descent, the origin of the other patients being Surinamese (9.4%), Antillean (4.3%), Moroccan (2.7%), Turkish (2.5%) or 'other' (14.6%). The median age of all patients was 30 years (range: 10 - 88). For men the median age was 33 years and for women 27 years.

Of all patients 2.5% were intravenous drug users in 1996, compared to 2.3% in the year 2000 ($p = 0.577$). The proportion of intravenous drug users among all patients was remarkably high in 1997, with 647 out of 4242 patients (15.3%). Among drug users 64% on average were female and 91% of all drug users were heterosexual.

HIV-testing

In total 14,800 patients (77.9%) were tested for HIV (Table 2). The percentage of patients who were tested for HIV increased from 2512 (75.9%) in 1996 to 3469 (88.1%) in 2000 ($p < 0.0005$). The percentage of anonymous testers increased over the years from 35.4% (890/2512) in 1996 to 55.7% (1931/3469) in 2000 ($p < 0.0005$), a trend which was seen among all groups of patients.

The percentage of new HIV cases diagnosed by an anonymous test was 22.2% (4/18) in 1996 and 53.3% (8/15) in 2000 ($p = 0.058$). Of the newly diagnosed HIV-patients 27.8% (5 out of 18) in 1996 and 53.3% (8 out of 15) in 2000 were tested before ($p = 0.139$). Most new HIV-cases (mean 41.6% of all cases) were found in the group of homo- and bisexual men, with the exception of 1998, when 66.7% (14/21) of the newly found HIV cases were heterosexual men and women.

The prevalence rate of HIV infection ranged from 0.4% (15/3469) in 2000 to 0.8% (24/2901) in 1997 and 1998. The median age of HIV-seropositive patients was 37 years, except in 1998 and 1999 when their median age was 34.

Among homo- and bisexual men the number of new HIV-cases decreased from 12 (6.0%) in 1996 to 7 (2.5%) in 2000 ($p = 0.09$). In women and heterosexual men significant changes could not be detected either.

STD-testing

Table 3 summarises the number of cases of gonorrhoea, chlamydia, NSU and early syphilis. The small group of patients who were classified as 'unknown' are not shown because of their few positive diagnoses.

Table 2. Number of HIV test and new HIV diagnoses related to gender, sexual orientation and intravenous drug use in 1996 - 2000; number and (%)

Table 2.	1996			1997			1998			1999			2000		
No HIV-test	798 (24.1)			1341 (31.6)			903 (24.4)			689 (18.1)			469 (11.9)		
HIV-test	2512 (75.9)			2901 (68.4)			2796 (75.6)			3122 (81.9)			3469 (88.1)		
type of testing	regular	anonym	unknow	regular	anonym	unknow	regular	anonym	unknow	regular	anonym	unknow	regular	anonym	unknow
	1611 (64.1)	890 (35.4)	11 (0.4)	1970 (67.9)	874 (30.1)	57 (2.0)	1872 (67.0)	903 (32.3)	21 (0.8)	1722 (55.2)	1289 (41.3)	111 (3.6)	1405 (40.5)	1931 (55.7)	133 (3.8)
tested earlier	397 (24.6)	141 (15.8)	4 (36.4)	653 (33.1)	194 (22.2)	12 (21.1)	817 (43.6)	280 (31.0)	5 (23.8)	670 (38.9)	385 (29.9)	42 (37.8)	613 (43.6)	695 (36.0)	46 (34.6)
heterosexual men	(n = 1198)			(n = 1097)			(n = 1204)			(n = 1300)			(n = 1410)		
	2 (0.2)			4 (0.4)			7 (0.6)			4 (0.3)			4 (0.3)		
homo- en bisexual men	(n = 201)			(n = 189)			(n = 223)			(n = 260)			(n = 278)		
	12 (6.0)			9 (4.8)			5 (2.2)			12 (4.6)			7 (2.5)		
type of testing	regular	anonym	unknow	regular	anonym	unknow	regular	anonym	unknow	regular	anonym	unknow	regular	anonym	unknow
	10 (83.3)	2 (16.7)	0	5 (55.6)	4 (44.4)	0	5 (100)	0	0	6 (50.0)	5 (41.7)	1 (8.3)	2 (28.6)	5 (71.4)	0
tested earlier	2 (20.0)	2 (100)	0	2 (40.0)	1 (25.0)	0	3 (60.0)	0	0	5 (83.3)	3 (60.0)	1 (100)	2 (100)	1 (20.0)	0
women (all)	(n = 1085)			(n = 1188)			(n = 1280)			(n = 1457)			(n = 1671)		
	3 (0.3)			4 (0.3)			7 (0.5)			2 (0.1)			3 (0.2)		
intravenous drug use (all)	(n = 19)			(n = 405)			(n = 64)			(n = 41)			(n = 54)		
	1 (5.3)			7 (1.7)			2 (3.1)			2 (4.9)			1 (1.9)		
unknown	(n = 9)			(n = 22)			(n = 25)			(n = 64)			(n = 56)		
	0			0			0			1 (1.6)			0		
total HIV-positive tests	18 (0.7)			24 (0.8)			21 (0.8)			21 (0.7)			15 (0.4)		
type of testing	regular	anonym	unknow	regular	anonym	unknow	regular	anonym	unknow	regular	anonym	unknow	regular	anonym	unknow
	14 (77.8)	4 (22.2)	0	17 (70.8)	7 (29.2)	0	14 (66.7)	7 (33.3)	0	11 (52.4)	8 (38.1)	2 (9.5)	7 (46.7)	8 (53.3)	0
tested earlier	2 (14.3)	3 (75.0)	0	3 (17.6)	1 (14.3)	0	3 (21.4)	2 (28.6)	0	5 (45.5)	3 (37.5)	2 (100)	5 (71.4)	3 (37.5)	0

The total number of gonococcal infections diagnosed increased from 98 (3.0%) in 1996 to 120 (3.3%) in 2000 ($p < 0.0005$). The number of gonococcal infections among heterosexual men increased from 52 (3.5%) in 1996 to 68 (4.4%) in 2000 ($p = 0.044$). There was also a rise in the number of cases of gonococcal cervicitis among heterosexual women from 22 (1.5%) in 1996 to 36 (2.0%) in 2000 ($p = 0.021$). Among homo-and bisexual men the number of gonococcal infections was 17 (6.6%) in 1996 and 22 (6.4%) in 2000 ($p = 0.658$). In 2000 tonsillar gonorrhoea was only diagnosed twice in the group of homo-and bisexual men.
The total number of chlamydial infections increased from 230 (7.0%) in 1996 to 375 (9.5%) in 2000 ($p < 0.0005$). This increase was observed both among heterosexual men (104 (7.0%) in 1996 versus 156 (10.0%) in 2000; $p < 0.0005$) and women(112 (7.8%) in 1996 versus 182 (10.1%) in 2000; $p < 0.0005$).
Among homo- and bisexual men a rise in chlamydial infections was seen from 9 (3.5%) to 29 (8.5%) ($p = 0.021$). More rectal chlamydial infections were diagnosed among this group, namely 2 in 1996 and 13 in 2000 ($p = 0.084$).
The total number of cases of early syphilis diagnosed decreased from 58 (1.8%) in 1996 to 16 (0.4%) in 2000 ($p < 0.0005$). Both among heterosexual men and heterosexual women the number of cases of early syphilis went down ($p < 0.0005$). In contrast, such a decline was not noted among homo- and bisexual men. The number of cases varied from 2 (0.8%) in 1996 to 6 (2.0%) and 4 (1.2%) patients in the years 1999 and 2000 respectively ($p = 0.473$). Among male intravenous drug users the number of syphilis infections ranged from none in 1996 to 10 out of 265 (3.8%) in the year 1997. Among female drug users the number of infections ranged from none in 2000 to 6 out of 380 (1.6%) in the year 1997. No statistically significant changes were seen in this group.
The number of cases of NSU diagnosed decreased from 242 (13.5%) in 1996 to 114 (5.8%) in 2000 ($p < 0.0005$).
Among heterosexual males the number of NSU cases went down from 206 (13.9%) in 1996 to 91 (5.8%) in 2000 ($p < 0.0005$). The number among homo- and bisexual men declined from 30 (11.7%) in 1996 to 19 (5.6%) in 2000 ($p = 0.016$).

Discussion

The increase in gonococcal and chlamydial infections in the STD clinic population as a whole is striking. A rise in the number of gonococcal as well as chlamydial infections was observed among heterosexual men and women. Homo-and bisexual men formed an exception, since only a significant increase in the number of chlamydial infections could be detected. A substantial decline of cases of early syphilis was seen, with – again - the exception of homo-and bisexual men. The number of newly diagnosed HIV infections has been rather stable during the five-year study period, in all tested groups. More HIV infections were found in the group of anonymously tested patients in 2000 compared with the year 1996. This can be explained by a significant rise in the percentage of STD clinic visitors being tested anonymously. The reasons for the growing percentage of people that were tested anonymously for HIV during the study period are not known. It could very well be that a growing perception of the

Table 3a. Gonorrhoea, chlamydia, NSU and early syphilis related to sexual orientation and intravenous drug use of all tested *male* patients in 1996 - 2000; numbers and (percentages).

	1996	1997	1998	1999	2000
heterosexual men					
TESTED	(n = 1480)	(n = 1488)	(n = 1499)	(n = 1539)	(n = 1563)
gonococcal infection	52 (3.5)	31 (2.1)	52 (3.5)	51 (3.3)	68 (4.4)
urethritis	52 (3.5)	31 (2.1)	52 (3.5)	51 (3.3)	68 (4.4)
proctitis	0	0	0	0	0
chlamydial infection	104 (7.0)	109 (7.3)	138 (9.2)	161 (10.5)	156 (10.0)
urethritis	104 (7.0)	109 (7.3)	138 (9.2)	161 (10.5)	156 (10.0)
proctitis	0	0	0	1	0
non-specific urethritis	206 (13.9)	156 (10.5)	167 (11.1)	158 (10.3)	91 (5.8)
TESTED	(n = 1480)	(n = 1485)	(n = 1499)	(n = 1437)	(n = 1504)
early syphilis	36 (2.4)	15 (1.0)	8 (0.5)	15 (1.0)	9 (0.6)
homo- / bisexual men					
TESTED	(n = 256)	(n = 271)	(n = 307)	(n = 309)	(n = 342)
gonococcal infection	17 (6.6)	15 (5.5)	25 (8.1)	26 (8.4)	22 (6.4)
urethritis	9 (3.6)	13 (4.8)	16 (5.2)	17 (5.5)	9 (2.6)
proctitis	9	2	11	10	14
chlamydial infection	9 (3.6)	20 (7.4)	18 (5.9)	26 (8.4)	29 (8.5)
urethritis	7 (2.7)	10 (3.7)	6 (2.0)	19 (6.2)	17 (5.0)
proctitis	2	10	13	12	13
non-specific urethritis	30 (11.7)	19 (7.0)	27 (8.8)	22 (7.1)	19 (5.6)
TESTED	(n = 256)	(n = 271)	(n = 307)	(n = 295)	(n = 328)
early syphilis	2 (0.8)	2 (0.7)	2 (0.7)	6 (2.0)	4 (1.2)
male iv-drug users					
TESTED	(n = 42)	(n = 265)	(n = 48)	(n = 20)	(n = 20)
gonococcal infection	0	8 (3.0)	3 (6.3)	0	0
urethritis	0	6 (2.3)	2 (4.2)	0	0
proctitis	0	2	1	0	0
chlamydial infection	0	11 (4.2)	4 (8.3)	0	0
urethritis	0	11 (4.2)	4 (8.3)	0	0
proctitis	0	0	0	0	0
non-specific urethritis	6 (14.3)	27 (10.2)	4 (8.3)	2 (10.0)	0
TESTED	(n = 42)	(n = 265)	(n = 48)	(n = 19)	(n = 19)
early syphilis	0	10 (3.8)	1 (2.1)	0	0

Table 3b. Gonorrhoea, chlamydia and early syphilis related to sexual orientation and intravenous drug use of all tested *female* patients in 1996 - 2000; numbers and (percentages).

	1996	1997	1998	1999	2000
heterosexual women					
TESTED	(n = 1439)	(n = 1747)	(n = 1657)	(n = 1692)	(n = 1804)
gonococcal infection	25 (1.7)	14 (0.8)	16 (1.0)	29 (1.7)	36 (2.0)
urethritis	22 (1.5)	13 (0.7)	16 (1.0)	29 (1.7)	36 (2.0)
proctitis	10	1	3	0	0
chlamydial infection	112 (7.8)	112 (6.4)	116 (7.0)	166 (9.8)	182 (10.0)
urethritis	112 (7.8)	112 (6.4)	115 (6.9)	166 (9.8)	182 (10.0)
proctitis	0	0	1	0	0
TESTED	(n = 1439)	(n = 1742)	(n = 1657)	(n = 1572)	(n = 1726)
early syphilis	19 (1.3)	10 (0.6)	9 (0.5)	5 (0.3)	3 (0.2)
homo- and bisexual					
TESTED	(n = 29)	(n = 31)	(n = 31)	(n = 61)	(n = 56)
gonococcal infection	0	0	1 (3.2)	1 (1.6)	1 (1.8)
urethritis	0	0	1 (3.2)	1 (1.6)	1 (1.8)
proctitis	0	0	0	1	0
chlamydial infection	1 (3.4)	2 (6.5)	4 (12.9)	11 (18.0)	3 (5.4)
urethritis	1 (3.4)	2 (6.5)	4 (12.9)	11 (18.0)	3 (5.4)
proctitis	0	0	0	0	0
TESTED	(n = 29)	(n = 31)	(n = 31)	(n = 57)	(n = 51)
early syphilis	0	0	0	0	0
female iv-drug users					
TESTED	(n = 42)	(n = 382)	(n = 110)	(n = 97)	(n = 71)
gonococcal infection	2 (4.8)	2 (0.5)	5 (4.5)	0	3 (4.2)
urethritis	2 (4.8)	2 (0.5)	4 (3.6)	0	3 (4.2)
proctitis	2	0	1	0	0
chlamydial infection	3 (7.1)	11 (2.9)	6 (5.5)	3 (3.1)	2 (2.8)
urethritis	3 (7.1)	11 (2.9)	6 (5.5)	3 (3.1)	2 (2.8)
proctitis	0	0	0	0	0
TESTED	(n = 42)	(n = 380)	(n = 110)	(n = 93)	(n = 62)
early syphilis	1 (2.4)	6 (1.6)	3 (2.7)	2 (2.2)	0

increasing risk of HIV infection due to unsafe sexual behaviour played a major role. The fact that there was a significant increase in the percentage of newly diagnosed HIV-positive homo- and bisexual men that were tested anonymously (from 16.7 in 1996 to 71.4% in 2000) makes this assumption likely. This rise of new HIV cases among the anonymously tested, was seen in the total population as well.

In The Netherlands, as in many other countries, more and more emphasis is being put on the testing for HIV of as many STD clinic visitors as possible. In future years we will attempt to motivate more patients to choose individual HIV testing, because of the possibility of initiating anti-retroviral therapy in an early stage, if indicated.

The proportion of intravenous drug users among all patients was unusually high in 1997. At the end of 1996 a syphilis epidemic occurred among IVDU street prostitutes in Rotterdam. To investigate the extent of the epidemic, active case-finding took place among all drug users. Clinics for drug users referred mainly to our STD clinic.[8]

The increase of gonorrhoea seen in our heterosexual patients is in line with data from Amsterdam.[9] Whereas in Amsterdam one found an increase in rectal gonorrhoea and syphilis among homo- and bisexual men, we did not observe an increase of gonorrhoea, including tonsillar infection, amongst this group.

The differences in STD rates among homo- and bisexual men between Amsterdam and Rotterdam may be explained by the assumption that the Amsterdam and Rotterdam gay population have their own - different - sexual network.

The growing prevalence of chlamydial infections indicates an increasing unsafe sexual behaviour of homo- and bisexual men. This was also the conclusion of the Amsterdam group.[2] The increasing number of chlamydial infections has to be interpreted with caution, taking into account especially the diagnostic methods used. The method used in 1996 has a significantly lower sensitivity compared to the one used in subsequent years (Gen Probe versus Cobas Amplicor PCR: less than 50 versus 96% sensitivity).[10,11] The prevalence rate of chlamydial infections found in 1997 was, however, lower than in 1996. In men, the prevalence rate increased from 6.3% in 1996 to 6.9% in 1997, which could be due to the test method. Nevertheless, the increasing trend of chlamydial infections in both men and women during subsequent years cannot be explained by a change in diagnostic method. The total number of chlamydial infections as well as the prevalence rates increased from 1997 to 1999, indicating a true increase. The decreasing number of cases of NSU can perhaps partially be explained by the more sensitive diagnostic method used for chlamydial infections. In the years after 1996 we observed a definite decrease compared to 1996. More urethritis cases were diagnosed as true *Chlamydia trachomatis* infections. However the significant decrease in the prevalence rate of NSU in the year 2000 cannot be explained.

There are no data with regard to patients' preference of STD care facilities in Rotterdam. A change in health care-seeking behaviour among the Rotterdam gay population is possible. However, to our knowledge no major changes in available STD care facilities have taken place in recent years.

In addition, the demographic characteristics among our patients did not change essentially. While we can not rule out some changes in the population tested, we do not think that the rise

in prevalence of STD can be explained by this factor.
Unsafe sexual contact with regard to STD transmission probably plays an important role in the rising trend seen.
Van Duynhoven and the European Study Group reviewed the trends in and risk groups for gonococcal infections in western Europe over the past decade. In most of Europe a decline was observed, with the exception of an increase in the Baltic countries in the early 1990s and an increase among men having sex with men between 1989 and 1991.[12,13] The London Gonococcal Working Group reported an alarming overall increase in the number of gonococcal infections diagnosed during the years 1997 and 1999.[14] In genitourinary medicine (GUM) clinics in London this rise already started in 1995/1996, where the prevalence of gonorrhoea almost doubled in the white population.[15]
Also in the United States, after a 13-year decline, the number of gonorrhoea cases in 1998 increased by 9% compared with 1997.[16]
The finding of a growing number of chlamydial infections is in line with observations made in other countries like the United Kingdom and Sweden.[17,18] In Sweden an increase in chlamydial infections among all young age groups (both sexes) was reported, which could not be attributed to a change in diagnostic methods.[18] A rising number of chlamydial infections and cases of syphilis among homo- and bisexual men is also seen in the United Kingdom.[17] This could indicate an increasing unsafe sexual behaviour in this group.
Among the largest group of our population tested, namely heterosexual men and women, a definite rise in the number of sexually transmitted diseases was observed. Further analyses of data, in order to detect specific high risk groups, is needed in order to be able to direct preventive activities. Co-operation with the division of Infectious Disease Control of the Rotterdam Municipal Health Service is of great importance in order to reach high risk groups and to co-ordinate preventive activities, such as health education and contact tracing.
Additional subgroup analyses should be done in order to get more information of sexual behaviour of high risk groups.

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prevalence of STD and HIV infections

chapter 4

Demographics, sexual behaviour and STD/HIV prevalence in two groups of men who have sex with men, in Rotterdam, The Netherlands

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Abstract

This study was performed to investigate whether men who have sex with men visiting the sexually transmitted diseases clinic, and those participating in a gay cohort were different with regard to demographic characteristics, sexual behaviour and sexually transmitted diseases (STD) / human immunodeficiency (HIV) virus prevalence. Data from men who have sex with men presenting at the sexually transmitted diseases clinic (group I; n = 318) were compared with data from men participating in a cohort (group II; n = 286). All males underwent a routine venereological examination. Men in group II were more often older ($p < 0.0005$), of Dutch descent ($p < 0.0005$) and had more sex partners ($p < 0.0005$). New cases of HIV infection were detected far more often in group I ($p = 0.04$). Also, urethral gonococcal infection was significantly more prevalent in group I ($p = 0.003$). Multivariate analyses showed that males presenting at the STD clinic (group I) were at higher risk for urethral gonorrhoea. The higher prevalence of HIV infection in group I was associated with a higher prevalence of recent STD, more concomitant urethral gonorrhoea infections at the time of visit, over 10 sex partners in the previous 6 months, and non-Dutch descent.

Introduction

Dutch and international reports have recently demonstrated dramatically increasing rates of gonorrhoea and syphilis, as well as an increase in sexual risk behaviour among men who have sex with men (MSM).[1-3]
Rotterdam is the second largest city in The Netherlands, with an estimated population of almost 700,000 individuals, living in and directly around the city. Few data have been published on sexually transmitted diseases (STD) and HIV prevalence and on sexual risk behaviour of MSM living in Rotterdam.[4-7]
Virtually all available information on sexual risk behaviour and the prevalence of STD and HIV among MSM derives from data on visitors to STD clinics.[8-10] It is almost impossible to recruit unbiased groups of MSM for research purposes, which means that enrolment of study participants is always prone to selection bias.
We performed the current study in Rotterdam to estimate the prevalence of STD and HIV in MSM and to analyse demographic and sexual behaviour characteristics. To investigate whether MSM visiting the STD clinic at their own initiative and those participating in a newly started gay cohort were different with regard to demography and sexual behaviour, the data of both groups were compared.
Comparison of these different groups of MSM allows for a more general assessment of behavioural indicators and possible risk factors for STD and HIV.

Methods
Design and procedures
The study took place at the STD clinic of the department of Dermatology and Venereology, Erasmus MC, Rotterdam, The Netherlands - the main facility in Rotterdam for people to be tested for STD. Persons with STD-related symptoms or sexual risk behaviour can be tested free of charge, and without being referred by a general practitioner. Data are routinely recorded in order to detect changes and trends in the epidemiology of STD at an early stage.[4,5]
Group I consisted of MSM who attended the STD clinic on their own initiative between January and December 1999. The data concern only the first visit during this recruitment interval. Group II consisted of MSM who were recruited to participate in the Rotterdam gay cohort study. Former (before 1999) visitors to the STD clinic were informed about the possibility of taking part in the study. Men visiting gay bars and saunas in Rotterdam - informed by trained volunteers – were also asked to join the study. In order to enrol a diversity of men, volunteers also visited so-called 'meeting places', where MSM have (anonymous) sex contacts. Advertisements were published in local mainstream as well as gay periodicals in order to interest potential participants. Participants in group II were enrolled between February 1999 and February 2000.
Cohort participants were asked to undergo testing for STDs and HIV every six months during a period of three years. Data from these participants concern only their first visit in the prospective study. Being willing to provide a blood sample was considered an inclusion

criterion for enrolment in group II. To recruit as many participants as possible, men could choose not to be informed about their HIV serostatus.

Data collection and questionnaires

Demographic and behavioural data collected for all men in group I and II included ethnic background, age, highest educational qualification, sexual orientation, age of first sexual experience, number of sex-partners during the previous six months, practice of anal intercourse, intravenous drug use, participation in prostitution and earlier diagnoses of STD or HIV infection. Self-administered questionnaires provided data from group II participants about condom use during sexual intercourse.

Patient investigation

Patients who had had sexual contact with at least one person of the same gender during the previous six months were considered homosexual. When sexual contact with a person of the opposite sex had taken place during the previous six months as well, they were recorded as bisexual.

All patients underwent a routine venereological examination using standardised procedures. Gonococcal urethritis was diagnosed by taking urethral swabs and, in case of urethral discharge, Gram-stained genital specimens for direct visualisation of diplococci. First-voided urine was used in testing for chlamydial infection.

Tests on rectal infections with gonorrhoea and chlamydia were carried out in all men in group II. In group I rectal sampling was performed only in the event of complaints of the rectum and/or when receptive anal sex had taken place during the previous six months.

Oropharyngeal tests for gonorrhoea were done in all men in both groups.

HIV-testing

Individual testing for HIV took place after counselling and after written informed consent had been obtained. Test results were personally given to the subjects involved. Those who did not want to know their serostatus were tested 'unlinked', in which case the blood sample was given a serial number that could not be linked to a certain individual. Unlinked testing is being done as part of an HIV sentinel surveillance program in The Netherlands. A leaflet handed out to all new patients explains the procedure of HIV testing beforehand.

Exceptions to routine HIV-testing were only made in group I when a patient refused any blood sampling or wanted to be tested selectively, e.g. for chlamydia only. New HIV cases were defined as positive test results in persons who either had never been tested before or had tested negative previously.

Laboratory methods

Blood samples were analysed for HIV-antibodies (micropartide enzyme immunoassay AxSym HIV-1/2 reagens; Abbott, Santa Clara, California, USA), syphilis (*Treponema pallidum* particle agglutination (TPPA)-test; Serodia-TPPA, Fujirebio Inc., Tokyo, Japan) and hepatitis B (anti-HBc and HBsAg, micropartide enzyme immunoassay IMX; Abbott, Santa Clara, Illinois, USA). Microbiological investigation included testing on gonorrhoea (Gram-stained genital;

GC-Lect agarplates; Becton & Dickson Europe, Meylan, France), *Chlamydia trachomatis* infection (Cobas Amplicor PCR, Roche Diagnostic Systems; Branchburg USA) and microscopy of first-voided urine for non-specific urethritis (NSU). NSU was defined as the presence of > 6 leukocytes per 10^{-6} litres of specimen of first-voided urine (KOVA-system; Hycor Biomedical Inc., Garden Grove, California, USA; in full accordance with the manufacturer's instructions).[11]

STD diagnoses

Gonorrhoea was diagnosed in the case of Gram-negative diplococci within polymorphonuclear leukocytes or in the event of a positive culture.

Patients with primary and secondary syphilis, and those with early latent syphilis, were categorised as having early syphilis. Early latent syphilis was diagnosed in patients without clinical signs, with a positive TPPA-test, a positive fluorescent treponemal antibody-absorption (FTA-abs) test and a positive Venereal Disease Research Laboratory (VDRL) test with a titre greater than or equal to 1:8. Subjects were asked for a history of previous treatment for treponematoses, a negative syphilis serology in the past and a recent history of syphilitic symptoms, in order to guarantee a correct classification.

Late latent syphilis was diagnosed in case of a positive TPPA-test, a positive FTA-abs test and a positive VDRL test with a titre below 1:8. Symptomatic as well as asymptomatic neurosyphilis was categorised as late syphilis.[12]

Individuals with HBsAg, with or without HBeAg, were categorised as having infectious hepatitis B, whilst past hepatitis B infection was defined as the presence of anti-HBc without HbsAg.

Statistical methods

Data were compared in order to assess statistically significant differences in the prevalence of STD and the number of new HIV cases in groups I and II. Prevalence was calculated as the number of positive tests per 100 tested individuals. For testing differences between the groups, the exact chi-square test was used, after all explanatory variables had been dichotomised. The test was considered significant if the p-value was less than 0.05.

Next, the prevalences of new HIV cases and of urethral gonorrhoea were compared between groups. In order to adjust for confounding variables, logistic regression analysis was used. The p-values in this analysis were based on likelihood ratio tests. The primary selection of covariables for entering in the model, along with group, was based on univariate analysis in two by two tables; an exact p-value below 0.05 was used. In the logistic regression model, the covariables with a p-value above 0.30 (based on the likelihood ratio method) were eliminated using a stepwise backwards elimination method.

Results

Demographic characteristics

Group I (MSM attending the STD clinic) consisted of 318 males, half of whom (51.0%) attended the clinic because of symptoms related to STD. Others (23.3%) wanted to be tested

on a regular basis, because of their sexual lifestyle. A small minority (3.6%) visited the STD clinic because of a new sexual relation or after referral by their general practitioner. In group II, 286 men were included, a minority of whom (less than 5%) had symptoms when they arrived for their first planned, semi-annual visit. The majority of these men, namely 189 (66.1%), had never visited the Rotterdam STD clinic before. Only 63 (22.0%) visited the STD clinic during the two years before their enrolment in the cohort study.
Table I summarises age, ethnic background, sexual orientation and highest educational qualification of both groups. In group I the median age was 34.5 years (range 13 - 74), while in group II it was 39.5 (range 18 – 75; $p < 0.0005$). In group I 81.3% of participants were of Dutch descent, compared to 93.0% in group II ($p < 0.0005$).

Sexual behaviour
Table II summarises sexual history and sexual behaviour of both groups in the previous six months. Due to a registration deficit there are different denominators in group I for 'number of partners in previous 6 months' and 'practised anal sex'. Group I participants had fewer sex partners during the previous six months, with a median number of 3 (range 0-99), compared to 7 (range 0-130) in group II ($p < 0.0005$).
There was no significant difference between the two study groups concerning practice of anal sex and type of anal sex practised. An earlier diagnosis of STD was reported by 53.3% men in group I and 63.3% in group II ($p = 0.02$).

STD/HIV prevalence
Table III summarises the prevalence of STD and HIV infection (new diagnoses) in both groups. Eleven persons in group I and 11 in group II who were already known to be HIV-positive when they visited the STD clinic ($p = 1.00$) were excluded from the analysis of HIV-testing. For various reasons (e.g. no blood samples taken; recent unlinked HIV test at earlier visit; administrative oversight) 41 males in group I were not tested for HIV. In group II two participants were not tested because of administrative oversight.
Of the 307 males in group I, 266 (86.6%) were tested for HIV; 151 (56.8%) of these men wanted an individual test and 115 (43.2%) were tested unlinked. In group II, 273 of the 275 (99.3%) were tested for HIV; 206 (75.5%) of these men wanted an individual test and 67 (24.4%) males were tested unlinked.
One-hundred-fifty-two (47.9%) of all men in group I and 159 (55.6%) of all men in group II had undergo earlier HIV-testing ($p = 0.61$).
In group I, 12 (4.5%) new HIV cases were diagnosed compared to 4 (1.5%) in group II ($p = 0.04$). Among individually tested persons, seven in group I (4.6%) and two in group II (1.0%) tested HIV-positive ($p = 0.04$). Of those who were tested unlinked, five (4.3%) persons in group I and two (3.0%) persons in group II were HIV-positive ($p = 1.00$).
New HIV cases were seen more often in persons of non-Dutch descent than in those of Dutch descent, namely 8.9% (7/79) versus 1.7% (9/522; $p = 0.002$). Of the total of 12 new HIV cases diagnosed in group I, 6 men were of non-Dutch descent. In group II, one of the 4

Table I. Demographic characteristics of the STD clinic visitors (group I) and the cohort participants (group II). Presented figures are numbers and (percentages).

Description	Group I *STD clinic visitors*	Group II *cohort participants*
	(n = 318)	(n = 286)
Age (years)	(n = 318)	(n = 286)*
≤ 19	9 (2.8)	1 (0.3)
20-24	25 (7.9)	12 (4.2)
25-29	57 (17.9)	24 (8.4)
30-34	68 (21.4)	55 (19.2)
35-39	45 (14.2)	51 (17.8)
40-44	41 (12.9)	50 (17.4)
45-49	23 (7.2)	33 (11.5)
≥ 50	50 (15.7)	60 (21)
Ethnic background	(n = 315)	(n = 286)*
Native Dutch	256 (81.3)	266 (93.0)
Surinamese	13 (4.1)	2 (0.7)
Antillean	7 (2.2)	2 (0.7)
Turkish	2 (0.6)	1 (0.3)
Moroccan	4 (1.3)	1 (0.3)
Other	33 (10.5)	14 (4.9)
Sexual orientation	(n = 318)	(n = 286)
Homosexual	261 (82.1)	251 (87.8)
Bisexual	57 (17.9)	35 (12.2)
Highest educational qualification	(n = 269)	(n = 286)
Primary/none	32 (11.9)	37 (12.9)
Secondary	124 (46.1)	127 (44.4)
Higher	113 (42.0)	122 (42.7)

* $p < 0.005$

Table II. Sexual history and sexual behaviour in previous six months of the STD clinic visitors (group I) and the cohort participants (group II).

Description	Group I *STD clinic visitors*	Group II *cohort participants*
	(n = 318)	(n = 286)
Number of partners in previous 6 months	(n = 273)	(n = 286)**
none	15 (5.5)	4 (1.4)
one	61 (22.3)	34 (11.9)
2-4	117 (42.9)	68 (23.8)
5-9	27 (9.9)	46 (16.1)
10-14	23 (8.4)	41 (14.3)
15-19	7 (2.6)	15 (5.2)
≥ 20	23 (8.4)	78 (27.3)
Practised anal sex	(n = 306)	(n = 286)
never	56 (18.3)	58 (20.3)
in previous 6 months	194 (63.4)	183 (64.0)
not in previous 6 months	56 (18.3)	45 (15.7)
Type anal sex practised (ever)	(n = 238)	(n = 228)
only receptive	44 (18.5)	45 (19.7)
only insertive	55 (23.1)	52 (22.8)
receptive and insertive	139 (58.4)	131 (57.5)
STD in previous 6 months (any)	(n = 315)	(n = 286)
	27 (8.6)	29 (10.1)
Ever had an STD	(n = 315)	(n = 286)*
	168 (53.3)	181 (63.3)
Worked as a prostitute in previous 6 months	(n = 313)	(n = 286)
	4 (1.3)	1 (0.3)
Had sex with a male prostitute in previous 6 months	(n = 309)	(n = 286)
	11 (3.6)	11 (3.8)
IV drug-use (ever)	(n = 310)	(n = 286)
	1 (0.3)	0 (0)

* $p < 0.05$

** $p < 0.005$

Table III. Prevalence of STD and HIV infection – new diagnoses - in the STD clinic visitors (group I) and the cohort participants (group II).

Description	Group I *STD clinic visitors*	Group II *cohort participants*
	(n = 318)	(n = 286)
HIV-tests (*)	(n = 266)	(n = 273)**
individual test	151(56.8)	206(75.5)**
unlinked test	115(43.2)	67(24.4)**
HIV antibody positive	12(4.5)	4(1.5)*
individual test	7(4.6)	2(1.0)*
unlinked test	5(4.3)	2(3.0)
Past hepatitis B (anti-HBc positive)	(n = 276)	(n = 228)
	31(11.2)	33(14.5)
Infectious hepatitis B (HBsAg positive)	(n = 276)	(n = 228)
	1(0.4)	0(0)
Early syphilis (a)	(n = 305)	(n = 281)
	6(2.0)	1(0.4)
Late syphilis (b)	(n = 305)	(n = 281)
	5(1.6)	3(1.0)
Gonococcal infection (*)	(n = 318)	(n = 286)
(any type)	26(8.1)	10(3.5)*
urethral gonorrhoea	17(5.3)	3(1.0)*
tonsillar gonorrhoea	2(0.6)	1(0.3)
rectal gonorrhoea (absolute numbers in group I)	10	7(2.4)
Chlamydial infection	(n = 318)	(n = 286)
(any type)	28(8.8)	23(8.0)
urethral chlamydial	21(6.6)	12(4.2)
rectal chlamydia (absolute numbers in group I)	12	16(5.6)
Non-specific urethritis	(n = 318)	(n = 286)
	23(7.2)	23(8.0)

(a) primary, secondary and early latent syphilis (VDRL ≥1:8)

(b) late latent syphilis and (a)symptomatic neurosyphilis

* $p < 0.05$; ** $p < 0.005$

Table IV. Multivariate analysis of explanatory variables in logistic regression model

'Presence of gonorrhoea' as dependent variable

Explanatory variable	p-value	OR	95% CI
HIV-positivity	0.64	1.71	0.21-14.00
Group	0.002	6.99	1.58-30.86

'New HIV-positivity' as dependent variable

Explanatory variable	p-value	OR	95% CI
Non-native Dutch descent	0.006	4.22	1.60-11.15
Over ten sex partners in past six months	0.016	2.89	1.21-6.91
Had an STD in past six months	0.016	3.56	1.33-9.53
Ever had an STD	0.26	1.82	0.63-5.29
Urethral gonorrhoea	0.014	6.82	1.68-27.67
Group	0.78	1.14	0.46-2.84

new HIV cases diagnosed was of non-Dutch descent. No significant differences were found when comparing the rate of STD in Dutch and non-Dutch males in both groups (p = 0.09). Gonococcal infection was found in 26 (8.1%) men from group I and in 10 (3.5%) participants from group II (p = 0.02). Seventeen patients from group I (5.3%) versus 3 patients from group II (1.0%) suffered from urethral gonorrhoea (p = 0.003). All males with urethral gonorrhoea had symptoms, i.e. urethral discharge and/or dysuria. The rate of tonsillar gonorrhoea did not differ significantly between both groups (0.6 versus 0.3%; p = 1.00). Rectal gonorrhoea was seen in 10 men in group I and 7 men from group II. We could not compare the prevalence because of the different criteria for testing in both groups. Only 4 of ten (40.0%) men in group I and 1 of seven (14.3%) in group II had rectal symptoms.
Chlamydial infections were seen in 28 (8.8%) persons from group I and in 23 (8.0%) from group II (p = 0.77). Twenty-one (6.6%) males from group I versus 12 (4.2%) from group II suffered from urethral chlamydial infection (p = 0.21). Urethral chlamydial infection was symptomatic (discharge and/or dysuria) in 15 of twenty-one (71.4%) men in group I and 5 of twelve men (41.7%) in group II. Rectal chlamydial infections were diagnosed in 12 men from group I and 16 men from group II. Again, we could not compare these numbers because of the different criteria for testing. Only 2 of 12 (16.7%) men in group I and 1 of 16 (6.3%) in group II had rectal symptoms (itching or painful sensations).

Univariate analysis was done to find associations between demographic characteristics, sexual behaviour and presence of urethral gonorrhoea and new HIV-positivity. After dichotomization the variables age (until 35 years or over), ethnicity (Dutch descent or non-native Dutch descent), sexual orientation (homosexual or bisexual), educational qualification (higher or primary/secondary), number of sex partners in past six months (until ten or over), practice of anal sex (never or ever), anal sex practised (only receptive or active/both), STD in previous 6 months (yes or no), ever had an STD (yes or no), group (I or II) and HIV-positivity or positive urethral gonorrhoea were used in these analyses. The presence of urethral gonorrhoea was significantly associated with HIV-positivity ($p = 0.011$; OR 5.76; 95%CI 1.79-18.55) and with belonging to group I ($p = 0.003$; OR 5.33; 95%CI 1.55-18.38). New HIV-positivity was significantly associated with non-native Dutch descent ($p = 0.021$; OR 2.83; 95%CI 1.20-6.68), over ten sex partners in previous six months ($p = 0.006$; OR 3.06; 95%CI 1.39-6.71), had an STD in previous 6 months ($p = 0.003$; OR 4.32; 95%CI 1.81-10.32), ever had an STD ($p = 0.030$; OR 2.74; 95%CI 1.09-6.86) and with positive urethral gonorrhoea ($p = 0.011$; OR 5.76; 95%CI 1.79-18.55).
Multivariate logistic regression was conducted to assess the independent contribution of univariately significant predictors of prevalence of urethral gonorrhoea and HIV-positivity (Table IV). The presence of urethral gonorrhoea was significantly associated with belonging to group I.
New HIV-positivity was significantly associated with non-native Dutch descent, over ten sex partners in previous six months, had an STD in previous 6 months and with positive urethral gonorrhoea.

Discussion

The data of both groups were compared to investigate whether MSM visiting the STD clinic at their own initiative and whether those participating in a newly started gay cohort were different in regard to demographic characteristics, sexual behaviour, STD and HIV prevalence.
To our knowledge, studies on differences in characteristics of these frequently studied types of samples have not been published previously. Comparison of characteristics is therefore useful for obtaining a broader view of behavioural indicators and possible risk factors.
Because of our method of recruitment of group II participants, this group contains former STD clinic patients, which could cause biased results. To reduce the risk of selection bias, we performed a series of multivariate analyses in a logistic regression model.
In our study we could not compare rectal infections because of the fact that different criteria for rectal testing were used in the groups investigated.

Our study showed that the males in the cohort (group II) were on average older, more often of Dutch descent and more often had an STD in the past. They also had more sex partners in the previous six months, but were less often diagnosed with a symptomatic STD in this period. HIV-seropositivity as well as urethral gonorrhoea were found significantly less often in group II. There was no difference in the prevalence of chlamydial infections between the groups.

It is not surprising to find more persons from group I than from group II presenting with a symptomatic STD. Their reason for calling in is mostly related to urethral symptoms. Multivariate logistic regression analyses (Tables IV) showed that presence of urethral gonorrhoea was significantly associated with 'group'. Group I had a higher risk of having urethral gonorrhoea. New HIV-positivity, used as dependent variable, was significantly related to urethral gonorrhoea, STD in previous six months, being of non-native Dutch descent and having had over ten sex partners in previous 6 months.
An important risk factor for a new HIV infection is a recent or concomitant STD. Of all 16 new HIV patients is this study, 4 (25%) either had a recent STD (previous six months) or a concomitant urethral gonorrhoea at the time of their visit. It is now well known that ulcerative and inflammatory STDs can facilitate HIV-transmission.[13]

An explanation for the higher number of STD and HIV infections in group I could be that more males from this group were of non-Dutch descent. This group may frequently or exclusively have sexual contact with persons from non-Dutch origin or perhaps recently migrated from endemic areas.[14] More prevalent STD in this group or these areas could possibly explain the higher rate of STD and HIV infection in group I.
Having had over ten sex-partners in the previous six months was associated with a higher risk of new HIV-infections. However, the number of sex partners does not seem to be the exclusive risk factor for HIV. In group II, one in two participants had had over 10 partners during the previous six months, while fewer new HIV-cases were seen here.
Males from group II seem to be more sexually active and more sexually experienced, based on their age, higher number of STD episodes in the past and frequent sex partner change. Males voluntarily participating in a cohort-study may be (very) cautious individuals, less at risk of getting an STD. This group is perhaps less at risk for STD or HIV infection because of precautions taken. According to the information from the self-administered questionnaires, 25.7% of all participants from group II who 'ever' had anal sex stated that they 'always' used condoms. Almost half of the participants (49,4%) having anal sex used condoms 'most of the time' and only 7.1% 'never' used condoms. In this study we could not compare both groups with regard to safe sex behaviour.

Another possible explanation for a more careful sexual behaviour among group II participants could be an earlier diagnosis of STD. Realising the nuisance of having an STD could be a reason for having safe sex more often. These hypotheses about more cautious sexual behaviour in group II participants voluntarily participating in our cohort suggest the need for a more detailed exploration of behavioural aspects in order to reveal useful information about possible precautions taken. Recently, we started a study using questionnaires among MSM visiting the STD clinic at their own initiative, as is done in the cohort study.

In conclusion, our study of two different groups of MSM found a higher prevalence of, mostly symptomatic, gonococcal infections in the group visiting the STD clinic at their own initiative. The higher prevalence of HIV infection in this group was related to the larger number of men

of non-Dutch descent and the higher prevalence of recent STDs and concomitant urethral gonococcal infection.
Safe sex messages, as well as active testing for HIV and STD, are both necessary as preventive measures. Continued monitoring of sexual behaviour and STD and HIV is important in MSM of both the cohort and the STD clinic in order to establish target groups for these preventive activities. Special attention should be paid to the group of MSM of non-Dutch descent.

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two groups of MSM

chapter 5

Human papillomavirus infection in men who have sex with men participating in a Dutch MSM-cohort study

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Abstract

Background: To develop strategies for prevention and early treatment of human papillomavirus (HPV) anal and penile cancer, a better understanding of related sexual behaviour risk factors is needed.

Goal: The goal of this study was to establish the prevalence of anal and coronal sulcus HPV in a group of men who have sex with men participating in a Dutch gay-cohort study, to identify risk factors associated with HPV infection in this group, and to investigate the presence of identical HPV types in couples with stable relationships.

Study Design: A cross-sectional study of 241 HIV-negative and 17 HIV-positive men who have sex with men visiting the sexually transmitted disease clinic of the Erasmus MC for a regular and scheduled examination. Participants underwent a routine venereological examination including HIV serologic analysis, and swabs were taken from the coronal sulcus and anus for HPV DNA testing. All subjects were asked to complete a questionnaire on sexual risk behaviour.

Results: HPV DNA was detected at the coronal sulcus in 23.5% of the HIV-positive men and in 15.8% of the HIV-negative men ($p = 0.492$). In anal specimens, HPV DNA was detected in 64.7% of the HIV-positive men and 32.8% of the HIV-negative men ($p = 0.015$). High-risk HPV types ($p = 0.007$) and 2 or more different HPV genotypes ($p = 0.006$) were seen more often in anal specimens of HIV-positive persons than in specimens of HIV-negative persons. A factor possibly associated with the presence of anal HPV infection was a concomitant anal infection with *Chlamydia trachomatis*, gonococci, or herpes simplex virus ($p = 0.059$). In only 16.7% of HPV-positive steady couples, both companions showed the presence of one or more identical HPV genotypes.

Conclusion: In this study, anal HPV DNA was detected more often than HPV DNA at the coronal sulcus. HIV positivity was associated with a higher prevalence of high-risk, but not with low-risk HPV types, at the anus. No association was found between HIV positivity and presence of high-risk HPV at the coronal sulcus. No sexual behavioural determinants for the presence of HPV could be identified. Concomitant anal infection with *Chlamydia trachomatis*, gonococci, or herpes simplex virus may be associated with HPV infection. In the majority of steady couples, partners were infected with different HPV types.

Introduction

Human papillomavirus (HPV) infections are the most common sexually transmitted viral infections and have a steadily increasing prevalence.[1] Genital warts or condylomata acuminata, one of the clinical manifestations of anogenital HPV infection, are predominantly associated with HPV types 6 and 11 and are estimated to affect about 1% of the sexually active population in the United States and Western Europe.[2,3] The estimated prevalence of subclinical and latent HPV infection in sexually active women and men ranges from 10% to 46%. Only 1% of all persons infected with HPV will have visible genital warts.[4] HPV is a double-stranded DNA virus. To date, more than 100 genotypes of HPV have been characterised. At least 35 of these genotypes have a predilection for the anogenital tract.[5] The virus infects the basal layer of the epithelium and increases cell proliferation and viral replication in fully differentiated keratinocytes. The arising papillomas are usually benign, but can progress to dysplasia or neoplasia in a small percentage of cases. The latter primarily occurs in case of infection with so-called high-risk types of HPV, particularly types 16 and 18.[6] The viral regulatory genes E6 and E7 inactivate the tumor-suppressor protein p53 and retinoblastoma (pRb) protein, which renders cellular DNA susceptible to carcinogenic effects of mutagens and increases the risk of malignant transformation.[7]
In almost all cervical cancers, HPV DNA (mostly HPV-16) has been identified.[5,8] The yearly incidence of anal cancer in the United States among both men and women in the general population is approximately one tenth that of cervical cancer. In men who have sex with men (MSM) with a history of receptive anal intercourse, the incidence of anal cancer was estimated to be at least 44 times higher, namely 35 per 100,000 per year.[5] The incidence of anal cancer among HIV-positive men may be about twice that of HIV-negative men. In a population-based study linking AIDS and cancer registries, the risk of anal cancer among persons with AIDS was 84 times greater than that in the general population.[9,10] Daling et al.[11] stated that a history of condylomata acuminata carried a relative risk of 27 for the development of anal cancer and anal sexual intercourse carried a relative risk of 50. According to Carter et al.,[12] HPV-16 seropositivity is associated with a six fold increased prevalence of anal cancer in men. Because anal condylomata acuminata are more common than penile warts in MSM, most studies on HPV in this group have focused only on anal warts and HPV infection.[9] However, 75% to 100% of patients with penile intraepithelial neoplasia have high-risk HPV DNA types, mostly HPV-16, whereas up to 50% of persons with invasive penile cancers test positive for HPV
DNA.[3,13,14] Penile cancer is most often of the squamous cell type and is less common in the United States and Western Europe than anal cancer, with a yearly incidence of 0.3 to 1.0 per 100,000. To the best of our best knowledge, there are no epidemiologic data on the possible association between HPV infection and penile cancer in (HIV-positive) homosexual and bisexual men. We consider information on the prevalence of HPV infection at the coronal sulcus important, because of the assumed relation with penile cancer.[13,14] However, there are no longitudinal studies on HPV-related penile disease in gay men. Therefore, we performed a cross-sectional study in a Dutch cohort of MSM to establish the prevalence of both anal and

coronal sulcus HPV infection and to identify sexual behaviour risk factors related to the presence of HPV infection. The presence of identical HPV genotypes in steady couples was also investigated. To develop strategies for prevention and early treatment of HPV-associated high-grade anal squamous intraepithelial lesions (HSIL), a better understanding of sexual behaviour risk factors is needed.[15]

Methods

Study Population and Study Design

The study was performed at the sexually transmitted disease (STD) clinic of the Department of Dermatology and Venereology, Erasmus MC, Rotterdam, The Netherlands. Beginning in February of 1999, we recruited MSM to participate in the Rotterdam cohort study. Homosexual and bisexual STD clinic attendees were informed about the opportunity to take part in the study. In addition, men visiting gay bars and saunas in Rotterdam were asked to participate in the study. To enrol a diverse group of men, trained volunteers visited so-called meeting places, where gay men have (anonymous) sexual encounters. Advertisements were published in newspapers and gay periodicals. The last participant was enrolled in February of 2000. Cohort participants were tested for STDs and HIV every 6 months for a period of 3 years. HPV specimens were taken only during the third visit. Therefore, the data reported in this article only concern the third visit of the cohort participants.

Data Collection and Questionnaires

Demographic and sexual behavioural data were collected. These included ethnic background, age, educational qualification, sexual orientation, number of sexual partners during the last 6 months, practice of anal intercourse, intravenous drug use, participation in prostitution, and earlier diagnoses of STD, including HIV infection. Additional data regarding age of first sexual experience, estimated number of lifetime sexual partners, and condom use were collected with self-administered questionnaires. Participants were asked if they had a steady sex partner for longer than 6 months; partners who answered this question positively were recorded as steady couples.

Venereological Examination

At enrolment and at each semi-annual visit, all participants underwent a standardised venereological examination as described previously.[16] In HIV-positive men, blood samples were taken for a CD4+ lymphocyte count.

HPV DNA Sample Collection

Between January of 2000 and August of 2001, specimens for assessment of HPV DNA were collected from all participants using a dry swab (Medical Wire & Equipment Co. (Bath) Ltd., Corsham, Wiltshire, United Kingdom) with sampling the coronal sulcus and the anal area.[17] In this study, we chose to sample the coronal sulcus for HPV. According to Holmes et al.,[18] condylomata acuminata in men first appear on the frenulum and coronal sulcus because the area is liable to trauma during intercourse, allowing entry of an infecting agent. The swabs were

immediately placed into standard collecting tubes without transport medium and sent to the Department of Virology for further processing.

Detection and Typing of HPV DNA

In 119 of the 258 men (46.1%), HPV DNA testing was performed by using a specific HPV-type detection polymerase chain reaction (PCR) for HPV types 6, 11, 16, 18, 31, and 33, as described elsewhere.[19] Later on, the SPF reverse-hybridisation line probe assay (LiPA) HPV PCR test, which detects 25 different HPV genotypes, was used in 139 of 258 males (53.9%). Kleter et al. showed that LiPA results were highly concordant with those of genotype-specific PCR tests.[20,21] The total nucleic acid DNA was extracted by using the total nucleic acid isolation kit on a Magna-Pure LC system (Roche Applied Science, Penzberg, Germany).

Statistical Methods

Data were compared to assess statistically significant differences in the prevalence of HPV related to sexual behaviour parameters. Prevalence was calculated as the number of positive tests per 100 tested individuals. Logistic regression analyses were used to test differences between the HPV groups. In these analyses, HIV status was included as a covariable along with the sexual behaviour parameters. We also tested whether HIV modified the effect of these sexual behaviour parameters. The result of a test was considered significant if the p value was less than 0.05.

Results

Population Characteristics

A total of 258 men were enrolled in this study, including 17 HIV-positive men (group I) and 241 HIV-negative men (group II). Of the 17 HIV-positive men, 3 were detected during the third semi-annual visit and had recently (less than 6 months) seroconverted. Fourteen subjects had tested positive for HIV before the study, within a median of 2 years (range, 1–9 years). Five HIV-positive men were on antiretroviral therapy. The median age of participants was 42.0 years (range, 29–59 years) in group I and 41.0 years (range, 19–76 years) in group II ($p = 0.772$). In group I, 94.1% of participants were of Dutch descent, compared with 93.8% in group II, a difference that was not significant. In group I, 88.2% of men were homosexual and 11.8% were bisexual, whereas 89.1% of men in group II were homosexual and 10.9% were bisexual; this difference was not significant. There were no significant differences between the groups in terms of educational qualification. No exact data were available regarding the circumcision status of the participants, but an estimated minority of less than 5% of these men were circumcised.

Sexual Behaviour Characteristics

Participants in group I had had more sexual partners during the last 6 months, with a median number of 15 (range, 2–78) compared with 8 partners (range, 0–140) in group II ($p = 0.031$). Not unexpectedly, the men in group I also had had more lifetime sexual partners, with a median number of 400 compared with 100 in group II ($p = 0.001$). In group I, no man had

Table 1. Detection of HPV in anal specimens in HIV-positive and HIV-negative MSM.

	HIV-positive MSM	HIV-negative MSM	p-values
both tests type	anal (n = 17)	anal (n = 241)	
HPV-positive (any type)	11 (64.7)	79 (32.8)	p = 0.015
HPV6-positive	4 (23.5)	30 (12.4)	n.s.
HPV11-positive	1 (5.9)	19 (7.9)	n.s.
HPV16-positive	5 (29.4)	22 (9.1)	p = 0.022
HPV18-positive	4 (23.5)	9 (3.7)	p = 0.006
HPV31-positive	4 (23.5)	18 (7.5)	p = 0.045
HPV33-positive	4 (23.5)	8 (3.3)	p = 0.005
two or more different	6 (35.3)	23 (9.5)	p = 0.006
only low-risk HPV (*)	1 (5.9)	30 (12.4)	n.s.
only high-risk HPV(**)	7 (41.2)	32 (13.3)	p = 0.007
LiPA PCR-Reverse test type	anal (n = 9)	anal (n = 130)	
HPV34-positive	0	0	-
HPV35-positive	0	5 (3.8)	n.s.
HPV39-positive	1 (11.1)	8 (6.2)	n.s.
HPV40-positive	0	4 (3.1)	n.s.
HPV42-positive	0	0	-
HPV43-positive	0	2 (1.5)	n.s.
HPV44-positive	1 (11.1)	7 (5.4)	n.s.
HPV45-positive	1 (11.1)	5 (3.8)	n.s.
HPV51-positive	1 (11.1)	6 (4.6)	n.s.
HPV52-positive	6 (66.7)	10 (7.7)	p < 0.0005
HPV53-positive	0	8 (6.2)	n.s.
HPV54-positive	0	2 (1.5)	n.s.
HPV56-positive	0	2 (1.5)	n.s.
HPV58-positive	0	0	-
HPV59-positive	0	3 (2.3)	n.s.
HPV66-positive	0	2 (1.5)	n.s.
HPV68-positive	3 (33.3)	10 (7.7)	p = 0.039
HPV70-positive	0	2 (1.5)	n.s.
HPV74-positive	0	2 (1.5)	n.s.
HPVXX-positive (***)	0	2 (1.5)	n.s.

Data are n and (%) of men testing positive for HPV

(*) low-risk HPV: HPV 6 and 11; (**) high-risk HPV: HPV 16, 18, 31 en 33; (***) unknown HPV-types

"never" had anal sex, whereas 15.5% of group II participants stated to have never practised anal sex; however, this difference was not statistically significant.
Data concerning condom use, which were collected using self-administered questionnaires, did not show significant differences between groups. Four of 16 men (25.0%) in group I and 48 of 204 men (23.5%) in group II said that they "always" used condoms during anal sex. No participants in group I and 13 of 204 men (6.4%) in group II participants said that they "never" used condoms. No significant differences were found between groups regarding age at first sexual experience with a male partner and participation
in prostitution or intravenous drug use (data not shown). Twenty-one steady couples participated in the current study, and none of these steady couples was mutually monogamous. Partners also had other sexual partners during the last 6 months, with a median number of 15 (range, 1–140).

Results of Venereological Examination
No differences regarding gonococcal, chlamydial, and herpes simplex virus infections, in the past or at the present visit, were found between the 2 groups. Reports of formerly diagnosed perianal and penile warts were similar in both groups. The median CD4+ lymphocyte count in HIV-positive men was 600 (range, 340–1,020). The median CD4+ count in the 5 HPV-negative men was 690 versus 490 in the 12 HPV-positive men, though this difference was not significant. CD4+ lymphocyte counts were not available for 3 of the 17 (17.6%) HIV-positive subjects.

HPV Detection
Table 1 summarises the detection of HPV in anal specimens in this cohort. HPV DNA was detected in coronal sulcus specimens of 4 (23.5%) out of 17 HIV-positive men and in 38 (15.8%) out of 241 HIV-negative men (p = not significant [NS]). In anal specimens, HPV DNA was detected in 11 (64.7%) out of 17 HIV-positive men and in 79 (32.8%) out of 241 HIV-negative men (p = 0.015). In HIV-positive men, HPV-16 was the most frequently HPV subtype detected in both anal and coronal sulcus specimens, and was found in 5 (29.4%) and 2 (11.8%) of these patients in the respective samples. In HIV-negative men, HPV-6 was the most frequently detected HPV subtype, and was detected 30 times (12.4%) in anal specimens and 12 times (5.0%) in coronal sulcus specimens.
In anal specimens, two or more different types of HPV were more often found in HIV-positive men than in HIV-negative men; namely, six times (54.5%) versus 23 times (29.1%; p = 0.006). With regard to coronal sulcus specimens, multiple HPV types were found once (25.0%) in the HIV-positive men versus eight times (21.1%) in HIV-negative men (p = NS). Only high-risk HPV types were found in the anal specimens of seven HIV-positive men (41.2%) and in 32 (13.3%) of the HIV-negative men (p = 0.007). In coronal sulcus specimens, only high-risk types were found in three HIV-positive men (17.6%) and in 19 (7.9%) of the HIV-negative men (p = NS). HPV-16 was detected more often in both coronal and anal specimens in HIV-positive men (p = 0.023). The simultaneous presence of only high-risk HPV genotypes

Table 2. Detection of HPV types 6 to 33 in *coronal sulcus* specimens and association with demographic characteristics, sexual behaviour and (past) STD diagnoses, adjusted for HIV-infection status.

	all participants (n = 258)		
characteristic	HPV negative (n = 216)	HPV positive (n = 42)	OR (95% CI)
age (years, mean ± SD)	41.5 ± 10.6	42.5 ± 9.7	1.01 (0.98 - 1.04)
lifetime male sexual partners (n)	median = 100	median = 100	
< 10	15 (6.9)	3 (7.1)	reference
10-50	69 (31.9)	8 (19.0)	0.57 (0.14 – 2.42)
51-200	56 (25.9)	16 (38.1)	1.41 (0.36 - 5.50)
> 200	64 (29.6)	13 (31.0)	0.97 (0.24 – 3.89)
age at first sex with male partner (years, mean ± SD)	18.0 ± 4.6	17.4 ± 4.2	0.97 (0.90 - 1.05)
history of penile warts	18 (8.3)	4 (9.5)	1.17 (0.38 – 3.67)
history of perianal warts	34 (15.7)	8 (19.0)	1.22 (0.52 – 2.88)
infection at present visit			
anorectal infection (HSV, GC,CT)	10 (4.6)	2 (4.8)	0.92 (0.19 – 4.51)
anal warts	4 (1.9)	2 (4.8)	2.76 (0.49 – 15.65)
CD4+ lymphocyte count x 10^6/l (mean ± SD) in HIV-positive participants	617.3 ± 197.7 (n = 11)	613.3 ± 270.1 (n = 3)	1.00 (0.99 – 1.01)
never had anal sex (n)	32 (14.8)	5 (11.9)	0.81 (0.29 – 2.23)
only receptive anal sex during last six months (n)	32 (14.8)	8 (19.0)	1.38 (0.56 – 3.43)
only insertive anal sex during last six months (n)	42 (19.4)	7 (16.7)	0.85 (0.35 – 2.07)
both insertive and receptive anal sex during last six months (n)	110 (50.9)	22 (52.4)	1.02 (0.52 – 2.00)
condom use during anal sex (n)			
never or sometimes	144 (66.6)	29 (69.1)	1.11 (0.54 – 2.26)
always	48 (22.2)	10 (23.8)	1.09 (0.50 – 2.39)

n = number; OR = odds ratio; SD = standard deviation; CI = confidence interval

HSV = herpes simplex virus; GC = gonococci; CT = *Chlamydia trachomatis*

Table 3. Detection of HPV types 6 to 33 in *anal* specimens and association with demographic characteristics, sexual behaviour and (past) STD diagnoses, adjusted for HIV-infection status.

	all participants (n = 241)		
characteristic	HPV negative (n = 168)	HPV positive (n = 90)	OR (95% CI)
age (years, mean ± SD)	41.3 ± 10.1	42.4 ± 11.1	1.01 (0.99 – 1.04)
lifetime male sexual partners (n)	median = 80	median = 140	
< 10	12 (7.1)	6 (6.7)	reference
10-50	58 (34.5)	19 (21.1)	0.64 (0.21 – 1.94)
51-200	48 (28.6)	24 (26.7)	0.98 (0.33 – 2.92)
> 200	44 (26.2)	33 (36.7)	1.34 (0.45 – 4.00)
age at first sex with male partner (years, mean ± SD)	17.8 ± 4.3	18.0 ± 4.9	1.01 (0.95 – 1.07)
history of penile warts	14 (8.3)	8 (8.9)	1.11 (0.44 – 2.78)
history of perianal warts	23 (13.7)	19 (21.1)	1.58 (0.80 – 3.12)
infection at present visit			
anorectal infection (HSV, GC,CT)	4 (2.4)	8 (8.9)	3.37 (0.95 – 11.9)
anal warts	0	6 (6.7)	NE
CD4+ lymphocyte count x 10^6/l (mean ± SD) in HIV-positive participants	713.3 ± 184.8 (n = 6)	543.8 ± 195.4 (n = 8)	1.00 (0.99 – 1.00)
never had anal sex (n)	30 (17.9)	7 (7.8)	0.43 (0.18 – 1.02)
only receptive anal sex during last six months (n)	28 (16.7)	12 (13.3)	0.75 (0.36 – 1.58)
only insertive anal sex during last six months (n)	30 (17.9)	19 (21.1)	1.34 (0.70 - 2.57)
both insertive and receptive anal sex during last six months (n)	80 (47.6)	52 (57.8)	1.39 (0.82 – 2.35)
condom use during anal sex (n)			
never or sometimes	111 (66.0)	62 (68.9)	1.12 (0.64 – 1.96)
always	36 (21.4)	22 (24.4)	1.19 (0.64 – 2.19)

n = number; OR = odds ratio; SD = standard deviation; CI = confidence interval; NE = not estimable

HSV = herpes simplex virus; GC = gonococci; CT = *Chlamydia trachomatis*

in coronal sulcus and anal specimens was found three times (17.6%) in HIV-positive men versus five times (2.1%) in HIV-negative men (p = 0.011).
In those specimens tested with the SPF LiPA HPV PCR test, HPV-52 was most frequently detected in anal specimens, and was detected in 16 of 139 (11.5%) patients. Anal HPV-52 was more often found in the nine HIV-positive men than in the 130 HIV-negative men; namely, 6 times (66.7%) versus 10 times (7.7%; p = 0.0005). HPV-68 was seen in 13 (9.4%) of all anal specimens: three times in HIV-positive men (33.3%) and 10 times in HIV-negative men (7.7%; p = 0.039). In coronal sulcus specimens, both HPV-68 and HPV-70 were most often found by using the LiPA test; this method detected these HPV subtypes in 6.5% of all men. HPV-68 was seen more often (three times) in HIV-positive men, i.e. (33.3%, p = 0.013).
In 18 of the 21 steady couples (85.7%), at least one partner was HPV positive. In 3 of these 18 couples (16.7%), both partners shared the same type of HPV infection. Seventeen of the 18 couples (94.4%) were discordant in terms of at least one HPV type.
The effect of risk factors, adjusted for HIV-infection status, on HPV types 6 to 33 in coronal sulcus and anal specimens is shown in Tables 2 and 3. Having a concomitant chlamydial, gonococcal, or herpetic infection may be a risk factor for having a positive anal HPV test result (p = 0.059). No other risk factors could be identified.
No relation was found between HPV risk and the variables Dutch descent, educational qualification, number of sex partners during the last 6 months, history of chlamydial, gonococcal, or herpetic anorectal infection, penile warts at present visit, or having had no anal sex during the last 6 months (data not shown in Tables 2 and 3). After including an interaction term between the risk factors and HIV infection in the model, no significant effect-modifying role of HIV could be found for all the explanatory variables listed in Tables 2 and 3, possibly because the number of HIV-positive participants in this study was small.

Discussion

In this study, we examined risk factors for the detection of coronal sulcus and anal HPV infections a Dutch cohort of MSM. Unlike most other studies, we also focused on coronal sulcus HPV infection, because of the assumed relation between HPV infection and penile cancer. In our study, HIV positivity was associated with a higher prevalence of anal high-risk HPV types, but not low-risk types. No association was found between the HIV serostatus and the prevalence of high-risk or low-risk coronal sulcus HPV infection. A limitation of this study is the small number of HIV-positive participants.
Factors associated with the presence of coronal sulcus HPV infection were not found. Possible risk factors associated with the presence of anal HPV infection could be a concomitant anal infection with *Chlamydia trachomatis*, gonococci, or herpes simplex virus. No sexual behaviour determinants for the presence of HPV could be found.

Other studies also found an association between HIV-positivity and a higher prevalence of anal high-risk HPV types.[9,22,23] In some studies, a relation between CD4+ counts lower than 200 x 10^6/l and high-risk HPV was detected as well.[9,22,23] However, other studies did not

confirm this finding.[24,25] It is unclear why we did not find an association between HIV serostatus and prevalence of high-risk coronal sulcus HPV. Van Doornum et al.[26] found more HPV-infections in swabs taken from the urethra than from the coronal sulcus in heterosexual men. In that study, which enrolled 65 Dutch heterosexual men with at least five heterosexual partners in the last 6 months, the presence of HPV DNA in coronal sulcus specimens was only 3%, whereas 17% of the urethral samples tested positive for HPV DNA.[26] Possibly swabs taken from the coronal sulcus often fail to detect prevalent HPV infections, perhaps because of penile hygienic measures. No exact data were available about the circumcision status of our study participants. In uncircumcised men, the maceration from epithelial debris and glandular secretions could possibly give rise to a more prevalent HPV infection or HPV persistence. An estimated number of less than 5% of men in this study were circumcised. A higher "natural" susceptibility of the anal skin and more frequently occurring trauma caused by receptive anal sex could explain the higher prevalence of HPV types at the anus. Mucoid anal discharge and moisture are easily retained within the natal cleft, and might be a reason for HPV persistence at the anal epithelium.
The concomitant presence of HIV and other STDs, some of which cause skin and/or mucosal defects (e.g., syphilis and genital herpes), has been described previously.[9,15,27,28] Mucosal defects may explain the higher prevalence of HPV in MSM with concomitant rectal STDs, as found in this study.

A number of studies have examined factors associated with the detection of anal HPV infection in MSM. These studies showed high rates of HPV infection among those who had practised receptive anal intercourse and had a large number of (lifetime) sexual partners. There also is an association between a high prevalence of anal HPV infection and trauma of the anal epithelium, younger age, rectal drug use, history of laxative use, hepatitis B infection, positive *Chlamydia trachomatis* serologic result, history of gonorrhoea, history of rectal discharge, anal fissures or fistulas, and smoking.[9,15,29]

In this study, the factors type of anal sex practised, age at first sexual experience with a male partner, and estimated number of (lifetime) sexual partners were not associated with the detection of anal HPV, contrary to results of other studies.[10,16] A recent study on the prevalence and determinants of genital HPV in heterosexual men could not detect an association of penile HPV infection and the factor age at first sexual intercourse. Also, no association was found between penile HPV infection and number of sexual partners.[29]
Risks factors for penile cancer are penile tear, being uncircumcised, difficulty in retracting foreskin, more than 30 lifetime sexual partners, condylomata acuminata, lichen sclerosus of the glans penis, smoking, ultraviolet A photograph chemotherapy, and smegma.[14]

The simultaneous presence of identical HPV types in steady couples was rarely seen. The majority (94.7%) of prevalent HPV types were not shared by both partners. The simultaneous presence of identical HPV types in steady couples is remarkably low. Rapid clearance, high numbers of sexual partners other then their steady partner, inadequate collection of specimens

and HPV-induced type-specific immunity could perhaps explain this finding. To get a better idea of clearance and persistence rates, all individuals participating in this study will be retested for the presence of HPV DNA after 1.5 years, during their sixth semi-annual visit. Concomitant anal infection with *Chlamydia trachomatis*, gonococci or herpes simplex virus might have been associated with anorectal HPV infection in this group.

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chapter 6

Acquisition and clearance of anal human papillomavirus infection in men who have sex with men participating in a Dutch MSM-cohort study

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Abstract

This study was performed to establish the prevalence of anal human papillomavirus (HPV) infection in relation to HIV-positivity in a group of men who have sex with men (MSM) and to correlate these data with regard to acquisition and clearance of HPV infection.

Data with regard to HPV-prevalence and HIV-serostatus during two visits were compared. At both visits participants underwent a routine venereological examination and swabs were taken from the perianal region for HPV-DNA testing.

During both visits HPV types 16, 18, 31, 33 and 52 were significantly more often detected in HIV-positive individuals. Persistence of HPV type 31 at the perianal region was significantly more often seen in HIV-positive MSM ($p = 0.036$) while the incidence of HIV type 16 may be associated with HIV-positivity ($p = 0.059$).

In HIV-positive MSM significantly more high-risk HPV types were detected at the perianal region and the tendency to persist is highest for HPV type 31.

Introduction

Human papillomavirus (HPV) infection is the most common sexually transmitted viral infection and has a steadily increasing prevalence (1). The prevalence of genital subclinical and latent HPV infection in sexually active women and men ranges from 10 to 46%, depending on country and population tested (2).
Anal cancer is not a common cancer in men in western European countries and the US. The incidence of anal cancer in the general population is approximately between 7 and 9 per million and has increased in recent decades (3,4). Anal cancer shares many features with cervical cancer, including a similar histology and a tendency to arise in the transformation zone, where the columnar epithelium changes to squamous epithelium (5). In 46 to 100 percent of all in situ and invasive squamous cell carcinomas of the anus, HPV-DNA has been identified (3,6,7). There is evidence that the HPV types that are causally linked to cervical cancer may also be linked to anal cancer. In a study in Denmark and Sweden, among 388 patients with invasive or in situ anal carcinomas in women and men, HPV-16 was detected by PCR in 73% (3). A large number of partners, young age at the time of first (receptive anal) sexual contact, unmarried status, a variety of concomitant (rectal) sexually transmitted diseases and a history of rectal genital warts are all linked to the risk of anal cancer (3).
Probably, only persistent infections may trigger carcinogenic development (8,9). Suppressed cellular immunity in HIV-positive persons and organ-transplant recipients receiving immunosuppressive therapy is associated with persistence of HPV infection in cervical cancer (10).
The incidence of anal cancer in men who have sex with men (MSM) was estimated to be at least 44 times higher than in the general population, while the incidence of anal cancer among HIV-positive MSM may be about twice that of HIV-negative MSM (11,12). In a population-based study linking HIV and cancer registries, the risk of anal cancer among persons with HIV was 84 times greater than in the general population (13-15). According to Del Mistro et al., HIV-infected MSM are at increased risk for persistent HPV infection (16).
Goldie et al. stated that screening HIV-negative MSM for preneoplastic anal lesions with anal cytology every 2 or 3 years, would provide life-expectancy benefits, and would be cost-effective. In HIV-positive MSM annual screening was found to be cost-effective (5,17).

Most HPV infections are transient; about 70% of infections with HPV are cleared within one year and as many as 91% are cleared within two years (18,19). The mean duration of high-risk HPV infection is longer than of low-risk HPV infection (8,9). Other data showed that HPV-DNA positivity may be more persistent for high-risk HPV types 16, 18, 31, 33 and 35 (20).

To develop strategies for prevention and early treatment of HPV-associated preneoplastic anal lesions (AIN) and anal carcinoma, a better understanding of clearance of HPV infection is needed. Knowledge of the prevalence of HPV in anal specimens could be the first step towards the development of an effective vaccine to prevent HPV-related anal carcinoma.

In this study data with regard to HPV-prevalence and HIV-serostatus of MSM at two planned cohort visits, with a median interval of 21 months, were compared. Data on the first visit were published elsewhere (21). The major goal was to study clearance and acquisition of anal HPV infection, and to investigate possible differences between HIV-positive and HIV-negative cohort participants.

Material and methods

Study population and study design

The study was performed at the STD clinic of the Department of Dermatology and Venereology, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, the Netherlands.

From February 1999 to February 2000, we recruited 286 MSM to participate in the Rotterdam cohort study. MSM were recruited by trained volunteers at gay meeting places like bars and sauna. Both HIV-positive and HIV-negative individuals were asked to join the study. The way participants were recruited has been described in more detail elsewhere (21). At enrolment, all participants provided written informed consent. The ethics committee of our medical centre approved the protocol.

Cohort participants were tested for STD and HIV every six months, during a period of three years. HPV-specimens were only taken during the third and sixth visit. During the third visit, a group of 258 men still participating in the cohort study (subcohort, 90.2% of the original cohort) was tested for HPV-DNA and during the sixth visit 213 men (82.6% of the subcohort). The median duration between the third and sixth visit was 21 months (range 7 – 32 months).

Data collection and questionnaires

Demographic and sexual behavioural data were collected. These included ethnic background, age, educational qualification, sexual orientation and number of sexual partners during the last six months. Also, data were collected about age of first sexual experience, estimated number of lifetime sexual partners and the presence of genital warts in the past by using self-administered questionnaires.

Venereological examination

At enrolment and at each semi-annual visit, all participants underwent a standardised venereological examination as described previously (22). In brief, the examination included testing for urethral, rectal and oropharyngeal gonorrhoea and urethral and rectal *Chlamydia trachomatis* infection. Blood samples were taken to be tested for HIV-antibodies, syphilis and hepatitis B. In HIV-positive men blood samples were taken for a CD4+ lymphocyte count every three months.

HPV-DNA sample collection

Specimens for assessment of HPV-DNA were collected using a dry swab (Medical Wire & Equipment Co. (Bath) ltd. Corsham, Wiltshire, United Kingdom), swabbing the perianal area. The swabs were immediately placed into standard collecting tubes without transport medium and sent to the department of Virology for further processing.
Between March 2000 and September 2001 all third visit specimens were taken and during the period January 2002 to May 2003 all sixth visit specimens.

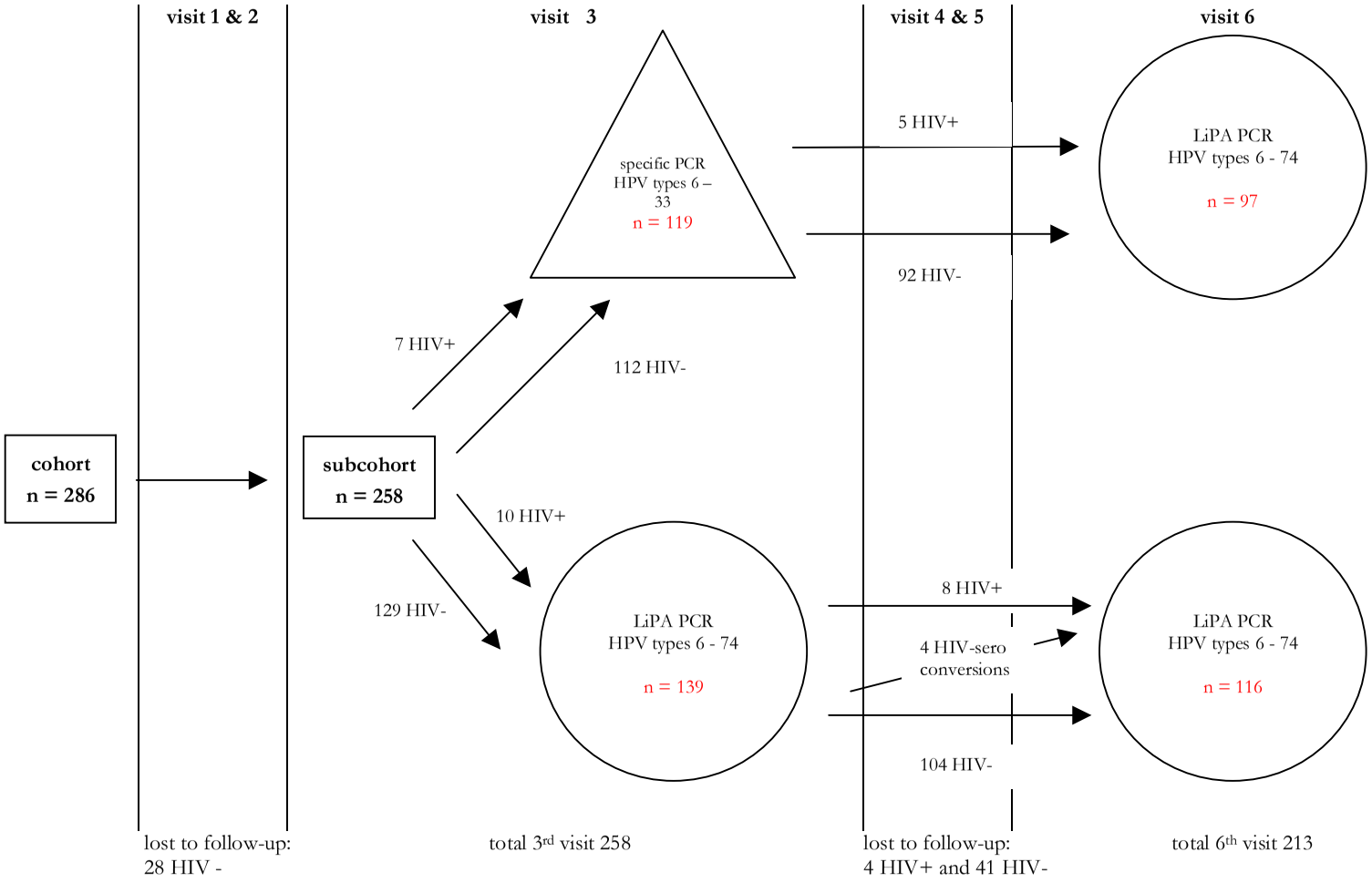
Detection and typing of HPV-DNA

During the third visit in 119 of the 258 men (46.1%) HPV-DNA testing was carried out by using a specific HPV type detection PCR for HPV-6, -11, -16, -18, -31 and -33, as described before (figure 1) (21,23). Later on, the SPF LiPA HPV-PCR-Reverse Hybridisation test, detecting 25 different HPV types, i.e. 6, 11, 16, 18, 31, 33, 34, 35, 39, 40 ,42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68, 70, 74 and 'unclassified' (XX), was used in 139 of 258 males (53.9%). Kleter et al. showed that LiPA results are highly concordant with those of genotype specific tests (24,25). The total nucleic acid DNA was extracted by using the total nucleic acid isolation kit on a MagnaPure LC system (Roche Applied Science, Penzberg, Germany).
We used the epidemiologic classification according to Munoz et al. (26), which grouped HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 83 as high-risk and considered types 26, 53 and 66 as probably high-risk. When in our study high-risk and low-risk HPV types were compared, HPV types 26, 53 and 66 were considered as high-risk types.
During the sixth visit, 213 participants were tested for HPV-DNA with the SPF LiPA HPV-PCR-Reverse Hybridisation test (figure 1).
Since two different HPV-detection methods were used, all individuals tested for HPV types 6 to 33 are, for analytical purposes, referred to as group A. Only those tested for HPV types 34 to 74 types at both visits are referred to as group B.

Statistical Methods

Data were compared in order to assess statistically significant differences in the prevalence of HPV related to HIV status. Prevalence was calculated as the number of positive tests by type per 100 tested individuals. Persistent cases of HPV were defined as cases which were prevalent at both visits. Fisher's exact test was used to test differences in prevalence of various HPV types between HIV-negative and HIV-positive MSM. A test was considered significant if the p-value was smaller than 0.05.
Incidence rates of infection with individual HPV types, and their associated 95% confidence intervals, were calculated on the basis of the numbers of cases in which a given type was detected among MSM at the sixth visit who were free of that type at the third visit. Calculation of the confidence intervals was based on the Poisson distribution.

Figure 1


visit 1 & 2
visit 3
visit 4 & 5
visit 6
cohort
n = 286
subcohort
n = 258
specific PCR
HPV types 6 – 33
n = 119
7 HIV+
112 HIV-
10 HIV+
129 HIV-
LiPA PCR
HPV types 6 - 74
n = 139
5 HIV+
92 HIV-
LiPA PCR
HPV types 6 - 74
n = 97
8 HIV+
4 HIV-sero conversions
104 HIV-
LiPA PCR
HPV types 6 - 74
n = 116
lost to follow-up:
28 HIV -
total 3rd visit 258
lost to follow-up:
4 HIV+ and 41 HIV-
total 6th visit 213

Results

Population characteristics

During the third visit, 258 men (subcohort) were tested, including 17 HIV-positive men and 241 HIV-negative men. During the sixth visit, 213 men were tested (82.6% of the subcohort), including 17 HIV-positive men and 196 HIV-negative men. None of the MSM refused anal testing for HPV-DNA.

Forty-five participants (17.4% of the subcohort) were only tested for HPV at the third visit, since they dropped out before the sixth visit. These participants were comparable to the rest of the subcohort with respect to sexual orientation (percentage bisexual: 20.0 versus 9.9%; p = 0.071), median number of sexual partners during the last six months (median number: 5 versus 8; p = 0.090) and median age at first sexual contact (median age both groups: 18 years, p = 0.39). Those who were not followed-up were significantly younger (median age 38 versus 43 years; p = 0.011), less often had a college degree (28.9 versus 48.0%; p = 0.021) and more often were of non-Dutch descent (11.1 versus 3.3%; p = 0.039).

Of the subcohort tested during the third visit, four HIV-positive men did not show up and could therefore not be tested for the second time. Of the 17 HIV-positive men tested at the sixth visit, four were detected since their third semi-annual visit and had therefore seroconverted recently. The median CD4+ lymphocyte count of all tested HIV-positive participants at the third visit was 600/mm^3 (range 340-1020) compared to 570/mm^3 (range 230-1100) at the sixth visit. During the third visit, only one HIV-positive MSM had a CD4+ lymphocyte count of ≤ 350/mm^3 compared to five HIV-positive MSM tested during the sixth visit. Viral loads were undetectable (RNA plasma viremia below 50 copies per millilitre) during the third visit in 5 MSM. The mean viral load in the other men was 4.1*10^4 copies per millilitre in the other participants.

During both visits, five of the 17 HIV-positive individuals were on antiretroviral therapy.

With regard to demographics, the 17 HIV-positive MSM at the third visit were comparable to the 241 HIV-negative MSM of the subcohort with respect to sexual orientation (percentage bisexual: 0 versus 12.4%; p = 0.23), age (median age: 43 versus 42 years; p = 0.80), ethnicity (MSM of non-Dutch descent: 5.9 versus 4.6%; p = 0.57), educational qualification (college degree: 33.3 versus 45.2%; p = 0.43), median age at first sexual contact (median age: 17 versus 18 years, p = 0.93) and median number of sexual partners during the last six months (median number: 10 versus 6; p = 0.074).

Of all HIV-positive MSM 5 (29.4%) stated to have had genital warts in the past versus fourty HIV-negative MSM (16.6%, p = 0.19).

During the third visit anal warts were found in six (2.3%) individuals compared to five (2.3%) MSM during the sixth visit. HPV-6 was detected in three and HPV-11 in five individuals. Surprisingly, in three of the MSM with anal warts no HPV could be detected at the perianal region.

In this study no data were available about cigarette smoking and circumcision status of the participants. An estimated minority of less than 5% of the participants were circumcised.

Table I. Detection of HPV types in anal specimens in HIV-positive and HIV-negative MSM at third and sixth visit.

detected HPV type	HIV-negative	HIV-positive	p-values	HIV-negative	HIV-positive	p-values
group A (a)	anal (n = 241)	anal (n = 17)		anal (n = 196)	anal (n = 17)	
HPV-6-positive	30 (12.4)	4 (23.5)	n.s.	22 (11.2)	4 (23.5)	n.s.
HPV-11-positive	19 (7.9)	1 (5.9)	n.s.	9 (4.6)	2 (11.8)	n.s.
HPV-16-positive	22 (9.1)	5 (29.4)	p = 0.022	19 (9.7)	6 (35.3)	p = 0.007
HPV-18-positive	9 (3.7)	4 (23.5)	p = 0.006	13 (6.6)	7 (41.2)	p < 0.001
HPV-31-positive	18 (7.5)	4 (23.5)	p = 0.045	4 (2.0)	5 (29.4)	p < 0.001
HPV-33-positive	8 (3.3)	4 (23.5)	p = 0.005	7 (3.6)	3 (17.6)	p = 0.036
group B (b)	anal (n = 129)	anal (n = 10)		anal (n = 104)	anal (n = 12)	
HPV-34-positive	0	0	-	2 (1.9)	0	n.s.
HPV-35-positive	5 (3.9)	0	n.s.	3 (2.9)	1 (8.3)	n.s.
HPV-39-positive	7 (5.4)	2 (20.0)	n.s.	2 (1.9)	3 (25.0)	p = 0.008
HPV-40-positive	4 (3.1)	0	n.s.	0	0	-
HPV-42-positive	0	0	-	1 (1.0)	0	n.s.
HPV-43-positive	2 (1.6)	0	n.s.	4 (3.8)	2 (16.7)	n.s.
HPV-44-positive	7 (5.4)	1 (10.0)	n.s.	7 (6.7)	4 (33.3)	p = 0.015
HPV-45-positive	5 (3.9)	1 (10.0)	n.s.	3 (2.9)	1 (8.3)	n.s.
HPV-51-positive	6 (4.7)	1 (10.0)	n.s.	11 (10.6)	4 (33.3)	p = 0.049
HPV-52-positive	10 (7.8)	6 (60.0)	p < 0.0005	5 (4.8)	4 (33.3)	p = 0.006
HPV-53-positive	7 (5.4)	1 (10.0)	n.s.	9 (8.7)	3 (25.0)	n.s.
HPV-54-positive	2 (1.6)	0	n.s.	1 (1.0)	0	n.s.
HPV-56-positive	2 (1.6)	0	n.s.	3 (2.9)	1 (8.3)	n.s.
HPV-58-positive	0	0	-	0	1 (8.3)	n.s.
HPV-59-positive	3 (2.3)	0	n.s.	5 (4.8)	1 (8.3)	n.s.
HPV-66-positive	2 (1.6)	0	n.s.	6 (5.8)	4 (33.3)	p = 0.010
HPV-68-positive	10 (7.8)	3 (30.0)	p = 0.053	5 (4.8)	1 (8.3)	n.s.
HPV-70-positive	2 (1.6)	0	n.s.	5 (4.8)	2 (16.7)	n.s.
HPV-74-positive	2 (1.6)	0	n.s.	7 (6.7)	0	n.s.
HPV-XX-positive (c)	2 (1.6)	0	n.s.	3 (2.9)	0	n.s.

(a) all individuals tested for HPV 6 to 33 at third visit using the specific HPV type detection PCR and at sixth visit with LiPA PCR

(b) only individuals tested for HPV 34 to 74 including unclassified types at third and sixth using LiPA PCR.

(c) unclassified HPV types

Table II. Frequency of HPV types in anal specimens in all MSM at third visit and cumulative positivity at sixth visit including ratio between frequency of positivity in both visits and that in one visit.

	prevalence at third visit (%)	cumulative positivity (%)	positive only once (%)	positive twice (%)	ratio twice/once
group A					
HPV-6-positive	29 (13.6)	41 (19.2)	27 (12.7)	14 (6.6)	0.5
HPV-11-positive	14 (6.6)	21 (9.9)	17 (8.0)	4 (1.9)	0.2
HPV-16-positive	25 (11.7)	40 (18.8)	30 (14.1)	10 (4.7)	0.3
HPV-18-positive	10 (4.7)	25 (11.7)	20 (9.4)	5 (2.3)	0.3
HPV-31-positive	19 (8.9)	26 (12.2)	24 (11.3)	2 (0.9)	0.1
HPV-33-positive	9 (4.2)	15 (7.0)	11 (5.2)	4 (1.9)	0.4
group B					
HPV-39-positive	8 (6.9)	11 (9.5)	9 (7.8)	2 (1.7)	0.2
HPV-44-positive	7 (6.0)	14 (12.1)	10 (8.6)	4 (3.4)	0.4
HPV-51-positive	5 (4.3)	17 (14.7)	14 (12.1)	3 (2.6)	0.2
HPV-52-positive	12 (10.3)	17 (14.7)	13 (11.2)	4 (3.4)	0.3
HPV-53-positive	7 (6.0)	18 (15.5)	17 (14.7)	1 (0.9)	0.1
HPV-68-positive	11 (9.5)	16 (13.8)	15 (12.9)	11 (9.5)	0.1

HPV-findings

Table I summarises the detection of HPV-DNA in anal specimens in HIV-positive and HIV-negative men during the third and sixth visit. Data on HPV-positivity at the third visit have been published elsewhere (21).

At the third visit, 90 of the 258 (34.9%) anal specimens in group A were positive for at least one HPV type compared to 78 of the 213 (36.6%) specimen at the sixth visit. Types most often detected were HPV-6 and 16 (13.2/12.2 and 10.5/11.7% respectively). Of the 139 MSM in group B tested at the third visit 60 (43.2%) were positive for at least one HPV type compared to 57/116 MSM (49.1%) at the sixth visit. Most often detected at the last visit were HPV-52 (11.5%), HPV-51 (10.8%), HPV-68 (9.4%), HPV-53 (8.6%) and HPV-44 (7.9%).

Table I shows that HPV-16, -18, -31 and -33 were detected in anal specimens significantly more often in HIV-positive participants during both visits. In group B only HPV-52 was detected significantly more often in HIV-positive MSM during both visits. HPV types 39, 44, 51 and 66 were significantly more often detected in HIV-positive individuals but only during the sixth visit.

During this sixth visit, two or more different types of HPV were more often found in anal specimens of HIV-positive men than in HIV-negative men, namely 14 times (82.4%) versus 66 times (33.7%; $p < 0.0005$). High-risk HPV types at the perianal region were found in 15 HIV-positive men (88.2%) and in 91 (46.4%) of the HIV-negative men ($p = 0.001$).

Cumulative HPV-positivity and persistence

The detection of the twelve most frequently detected HPV types in anal specimens at the third visit and the cumulative HPV-positivity for each HPV type and for low-and high-risk HPV types is summarised in table II. Only the 12 most common types (those with ≥ 7% cumulative positivity) were included in the analyses. HPV-16 was the most common type cumulatively (n = 40; 18.8%) in group A and HPV53 in group B (n = 18; 15.5%).

Table II also classifies HPV types on the basis of the tendency for a given type to persist during both visits. The right-hand column in the table shows the ratio between the frequency of positivity in both visits and that in one visit, as an indication of the tendency of a given type to persist. The ratio for all HPV types is smaller than one. The ratio for HPV-6 was 0.5, indicating that an HPV-6 infection was twice as often detected at only one of the two test visits.

Table III summarises the tendency to persist of the twelve most frequently detected anal HPV types in HIV-positive and HIV-negative men. It shows that the tendency of HPV-31 for being persistent was significantly stronger in HIV-positive MSM (p = 0.036).

Table III. Ratio between frequency of positivity in both visits and that in one visit of HPV infection at anal region in both HIV-positive and HIV-negative MSM.

	ratio twice/once in HIV-positive MSM	ratio twice/once in HIV-negative MSM	p-value
group A			
HPV-6-positive	3/2 (1.5)	11/25 (0.4)	n.s.
HPV-11-positive	0/1 (0.0)	4/13 (0.2)	n.s.
HPV-16-positive	2/5 (0.4)	8/24 (0.3)	n.s.
HPV-18-positive	3/3 (1.0)	2/15 (0.1)	n.s.
HPV-31-positive	2/3 (0.7)	0/19 (0.0)	0.036
HPV-33-positive	2/2 (1.0)	2/8 (0.3)	n.s.
group B			
HPV-39-positive	1/2 (0.5)	1/5 (0.2)	n.s.
HPV-44-positive	0/2 (0.0)	3/6 (0.5)	n.s.
HPV-51-positive	1/1 (1.0)	1/12 (0.1)	n.s.
HPV-52-positive	1/4 (0.3)	2/8 (0.3)	n.s.
HPV-53-positive	0/3 (0.0)	1/13 (0.1)	n.s.
HPV-68-positive	0/3 (0.0)	1/9 (0.1)	n.s.

Incidence of HPV infection

HPV-51 was the most frequent incident type (0.52%/month), followed by HPV-53 and HPV-16 (0.48 versus 0.37%/month). The incidence of anal HPV-16 infection could possibly be associated with HIV-positivity (p = 0.059; see table IV).

Table IV. Incidence of anal HPV infection in both HIV-positive and HIV-negative MSM.

	rate/1000 person-months (95% CI) HIV-positive MSM	rate/1000 person-months (95% CI) HIV-negative MSM	p-value
group A			
HPV-6-positive	4.9 (0.1-27.4)	3.0 (1.5-5.3)	0.95
HPV-11-positive	0.0 (0.0-11.3)	1.2 (0.4-2.9)	1.45
HPV-16-positive	15.2 (3.1-44.5)	2.9 (1.5-5.2)	0.059
HPV-18-positive	10.3 (1.2-37.0)	2.7 (1.3-4.8)	0.23
HPV-31-positive	9.4 (1.1-33.9)	1.0 (0.3-2.6)	0.068
HPV-33-positive	0.0 (0.0-15.7)	1.2 (0.4-2.8)	1.60
group B			
HPV-39-positive	8.1 (0.2-45.3)	0.5 (0.1-2.7)	0.22
HPV-44-positive	6.5 (0.2-36.4)	1.9 (0.5-4.9)	0.60
HPV-51-positive	6.6 (0.2-36.9)	4.7 (2.3-8.7)	1.07
HPV-52-positive	11.1 (0.3-61.9)	1.5 (0.3-4.3)	0.31
HPV-53-positive	14.2 (1.7-51.2)	3.9 (1.7-7.7)	0.26
HPV-68-positive	0.0 (0.0-27.3)	1.9 (0.5-4.9)	1.62

Discussion

In this study we examined the persistence and incidence of anal HPV infection in a Dutch cohort of MSM, and showed that HPV infection was relatively frequent: up to 50% of all MSM tested for HPV infection in group B at the perianal region were positive for one or more of these HPV types. Nearly 40% of the HIV-positive participants tested were HPV-16 or HPV-18 positive at the perianal site during both visits. During this visit two or more different types of HPV were more often found in anal specimens of HIV-positive men than in HIV-negative men. Most common HPV infections at the perianal site were HPV-6, -16 and -51. The high-risk HPV-51 was the most frequent incident type in this study (0.52%/month). The incidence of anal HPV-16 infection showed a strong tendency towards association with HIV-positivity. In HIV-positive MSM the tendency to persist was significantly higher for HPV type 31 at the perianal region, as compared to HIV-negative MSM.

It is unlikely that variability in sample collection can explain the differences in HPV detection. During both visits, more than 90% of all anal HPV specimens were collected by the same physician. All other men were, during both visits, examined by the same, thoroughly instructed, research nurse.
Given the fact that MSM from the Rotterdam region were invited to join the cohort, it is most likely that the cohort participants were not representative of the MSM population at large in the Netherlands. One of the major limitations of our study is the relatively small number of HIV-positive individuals, however this is in concordance with the modest rate of HIV-seropositivity amongst MSM in the Netherlands (27).
Another important issue in this study is that we cannot measure true persistence among those positive for a specific HPV type at enrolment. As yet it is still impossible to distinguish a new infection with a certain HPV type from a persistent infection, within the limitations of the HPV detection method. For this reason we can only measure the 'presumed' persistent rate of those positive at enrolment. Maybe type specific serology will enable discrimination between a new infection and persistent infection in the future.
It is, however, important to conclude that a high incidence and a higher tendency to persist of high-risk anal HPV infection (HPV-31 in this study) may be a reason for more frequent HPV-related disease in HIV-positive MSM.
Our results are largely in accordance with the study on the prevalence of cervical HPV infection by Franco et al., in which they showed that in a group of 1425 low-income women in a high-risk area for cervical cancer the mean infection duration was longer for high-risk HPV types (8).
In the HIV-positive cohort participants a significant higher persistence of high risk HPV type 31 was seen but not of other high-risk types or low-risk HPV types. We can not explain why no significant association between HIV-positivity and the more oncogenic HPV type 16 could be found in this study. Richardson et al. found that HPV type 16 was the most persistent, followed by HPV-31 and HPV-53 in cervical specimen of more than 600 female university students in Montreal, Canada (28).
High prevalences of high-risk HPV types, as found in HIV-positive individuals in this study (40% anal HPV-16 or HPV-18 positivity), may go together with a high detection rate of abnormal anal cytology (29). In our study, after a follow-up period of a median number of 21 months, HPV-related carcinoma in situ (AIN III) was detected in two MSM after careful clinical inspection of the anal region followed by histopathology. One other man died of metastatic rectal adenocarcinoma, located 7 centimetres above the anal sphincter. Although this man was found to be HPV-16 positive at the anal region during both visits, no HPV DNA was detected in the biopsy of the adenocarcinoma. Anal cancer screening should be promoted, especially in HIV-positive individuals, to prevent HPV-related malignancies (5,17,30,31).
Understanding the epidemiology of anal HPV infection is important for the prevention of HPV-related disease in MSM. Longitudinal studies in different geographic areas may provide information which can also be used for prevention and future immunisation programs (32). Further studies in MSM are needed to establish additional risk factors related to HPV-persistence.

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chapter 7

Incidence of STDs and HIV infection related to perceived HIV/AIDS threat since HAART availability in men who have sex with men

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In press Sexually Transmitted Diseases

Abstract

Objectives: Concerns have been expressed regarding increase in risky sex because of the availability of antiretroviral treatments in western countries

Goal: The goal of this longitudinal study was to investigate the association between HAART- and PEP-related beliefs and the incidence of STDs and new HIV infection in men who have sex with men (MSM).

Study Design: Data on the incidence of STDs and new HIV infection, and the level of agreement with different HAART- and PEP-related beliefs from 151 HIV-negative MSM were compiled.

Results: Of all MSM, 65.6% tested negative for any STDs and 7 men HIV seroconverted. Perceiving less HIV/AIDS threat since HAART availability, and younger age were significantly associated with a higher incidence of STDs. Perceiving less need for safe sex since HAART availability was significantly associated with an increased likelihood of HIV seroconversion.

Conclusions: The results support the assumption that there is an association between the incidence of STDs and a decreased perception of HIV/AIDS threat due to HAART availability. Less perceived need for safe sex since HAART availability was associated with HIV seroconversion.

Introduction

In 1995, the first case-control study showed that treatment with zidovudine after exposure to HIV decreased the risk of infection by 79 percent.(1) Since then, several reports warned for a potential increase in risky sexual behaviour because of the widespread availability and use of effective antiretroviral treatments by men who have sex with men in western countries. Studies in MSM in San Francisco who engaged in high-risk sex reported that some men had less concern of becoming HIV-positive, because of the availability of antiretroviral therapy.(2,3)

Cross sectional studies on larger samples of respondents also reported that important minorities of MSM changed their perceptions of HIV infection and protective behaviour. For instance, in a community sample of 379 MSM who reported awareness of antiretroviral therapy regimens, 10% of the respondents (strongly) agreed with the statement that 'AIDS is now very nearly cured' and 13% felt that 'the threat of AIDS is less serious now than in the past'. Overall 8% of all MSM and 18% of HIV-positive MSM on antiretroviral therapy said that they practised safe sex less often because treatments had advanced.(4)
In Chicago, 46% of 554 MSM, recruited during the course of a 'gay'-orientated street fair, reported unprotected anal sex in the past 6 months. Lowered concern for HIV infection, reflecting the impact of antiretroviral treatment, emerged as an independent predictor of unprotected anal sex. The authors warned that even a small degree of lowered concern may be associated with substantial changes in rates of HIV transmission.(5)

In recent years, a large increase in gonorrhoea and early syphilis was reported in MSM in several cities such as San Francisco, London, Sydney and Amsterdam.(6-10) These trends indicate a change in sexual behaviour, possibly as a result of the introduction of highly active antiretroviral therapy (HAART).(10,11) Data from a cohort study in Amsterdam showed that HIV-positive and HIV-negative MSM practised anal sex more often in the period after the introduction of improved antiretroviral therapies. The proportion of men who had unprotected anal sex increased among HIV-negative men.(10,11,12)
Elford et al. recently suggested that optimism due to the availability of HAART is unlikely to explain the increased high-risk sexual behaviour in MSM over time.(13) It was stated that most studies report cross sectional associations between optimism and self-reported anal sex rather than longitudinal data. In their longitudinal study among almost 3000 MSM using London gyms, Elford et al. suggested that the upward trend in self-reported high-risk behaviour might be explained by increased sex seeking on internet, an increased opportunity for meeting sexual partners in saunas and backrooms and the possibility that MSM have become accustomed to the risk of HIV infection after two decades of AIDS.
A recent prospective study from Amsterdam in MSM showed that a tendency towards agreement with 'perceiving less HIV/AIDS threat' predicted individual's change to unprotected receptive anal intercourse over time.(14) The authors concluded that the data

supported the hypothesis of a causal relation between decreased HIV/AIDS threat and a change to unsafe receptive anal intercourse at an individual level.
A relation between HIV optimistic MSM and self-reported unprotected anal intercourse with casual partners was also found by Williamson et al. However, after multivariable logistic regression, controlling for confounding factors as survey year, the authors concluded 'our results strongly suggest that HIV optimism can not explain recent high-risk sexual behaviour among Scottish MSM'.(15)

Concerns have equally been expressed regarding the possibility that the availability of postexposure prophylaxis (PEP) may lead people to have unsafe sexual intercourse in the belief that they were protected from infection if they used PEP.(16,17)
In a study in the gay community of San Francisco, Waldo et al. reported a small percentage of men who had sex with men (MSM) and who self-reported that availability of PEP increased their risky sexual behaviour.(17)
Very recently, a study among almost 400 mostly MSM (92%) who used PEP after sexual exposure (95%) or injection drug exposure showed, after five sessions of risk-reduction behavioural counselling, an increase in high-risk sexual intercourse in 14% of the men after a 12 months follow-up.(18)

The aim of this study was to prospectively investigate the association between HAART- and PEP-related beliefs and cumulative new STD and HIV infections among HIV-negative MSM participating in the ongoing Rotterdam cohort study. In this study we focused on STD/HIV diagnoses rather than data on self-reported unprotected sexual contacts. Data on the prospective relation between optimism due to HAART and PEP and new STD and HIV infections among HIV-negative MSM provide an important insight into this extensively debated and investigated issue.

Materials and Methods

Study population and study design

The study was conducted at the STD clinic of the Department of Dermatology and Venerology, Erasmus MC, University Medical Centre Rotterdam, The Netherlands.

From February 1999 onwards, we recruited 286 MSM to participate in the Rotterdam MSM-cohort study. Both HIV-positive and HIV-negative MSM were recruited by trained volunteers at gay meeting places like bars and saunas and with the use of advertisements in newspapers and gay periodicals. The way participants were recruited has been described in more detail elsewhere (19). At enrolment all participants provided written informed consent. The ethics committee of our hospital approved the protocol. Cohort participants were tested for STD and HIV every six months. In case of STD symptoms in between two biannual cohort visits, participants were urged to visit the STD clinic at short notice.

Inclusion criteria for the present study were having had sex with at least one male partner in the preceding twelve months, being HIV-negative at enrolment and participating in five successive cohort visits, starting with visit number 3, which took place between January 2000 and September 2001.

The questionnaire measuring beliefs concerning PEP and HAART was first introduced at the third cohort visit.

A total of 151 HIV-negative MSM who participated in all five successive biannual cohort visits (visit numbers 3 to 7), between January 2000 and April 2003, were included in this study.

Data collection and questionnaires

At each visit medical history was taken, including self-reported information on STDs in the past 6 months. Also, demographic and sexual behaviour information was collected including ethnic background, age, educational level (defined as 'low' with school attendance up to the age of about 16 years, as 'middle' with school attendance up to the age of about 18 years, and as 'high' with a college degree or equivalent), sexual orientation and number of sexual partners during the previous six months. Participants further completed self-administered questionnaires on behavioural and psychological issues related to STDs, HIV and AIDS during the five consecutive visits. During the third visit, participants were asked to complete a standardised behavioural questionnaire that included a total of 24 statements concerning PEP and HAART. Statements were selected from other studies.(7,17,20)

HAART-related beliefs

Seventeen items, measured with a five-point rating scale ranging from 1 ('strongly disagree') to 5 ('strongly agree') assessed participants' HAART-related perceptions.

Using principal components analysis (PCA) with varimax rotation (assuming no correlation between the factors), we distinguished four principal components (Table I), each consisting of several related statements. The cumulative variance explained by the four components was 62.4%.

Reliability analysis was used to confirm internal consistency of scales constructed on the basis of identified principal components. Scores on each principal component were calculated as the

average scores of the statements involved and ranged from 1 to 5. Odds ratios were calculated per unit increase of the average scores.
The first principal component, *perceiving less HIV/AIDS threat since HAART availability,* explained 19.7% of the variance and consisted of five related statements with a reliability of 0.84 (Cronbach's alpha). The second principal component, *perceiving less need for safe sex since HAART availability,* explained 16.4% of the variance and consisted of three related statements with a reliability of 0.93. The third principal component, *general beliefs concerning the start of HAART,* explained 13.8% of the variance and consisted of four related statements with a reliability of 0.73. The fourth principal component, *perceiving high effectiveness of HAART in curing HIV/AIDS,* explained 12.5% of the variance and consisted of two related statements with a reliability of 0.80.

Table I. Principal components of HAART-related beliefs and concerned statements identified among MSM-cohort in Rotterdam.

perceiving less HIV/AIDS threat since HAART availability (Cronbach's alpha: 0.84)
I am less threatened by the idea of being HIV-positive than I used to be
I am less worried about HIV infection than I used to be
I think HIV/AIDS is less of a problem than it used to be
I think HIV/AIDS is a less serious threat than it used to be because of new HIV/AIDS treatments
I am less concerned on becoming HIV-positive myself because of new HIV/AIDS treatments
perceiving less need for safe sex since HAART availability (Cronbach's alpha: 0.93)
I think that condom use during sex is less necessary now that new HIV/AIDS treatments are available
I think that someone who is HIV-positive now needs to care less about condom use
I think that the need for condom use is less than it used to be because you can always start new treatments
general beliefs concerning the start of HAART (Cronbach's alpha: 0.73)
Now new HIV/AIDS treatments are available, it is more important to know your HIV status
Start with new HIV/AIDS treatment is necessary as soon as you are HIV-positive
Early start with new HIV/AIDS treatment is necessary even when someone is HIV-positive without complaints or symptoms
It is necessary to know your HIV status in order to start with new HIV/AIDS treatment as soon as you are HIV-positive
perceiving high effectiveness of HAART in curing HIV/AIDS (Cronbach's alpha: 0.80)
I think that someone who is HIV-positive and uses new HIV/AIDS treatments can be cured
I think that new HIV/AIDS treatments can eradicate the virus from your body

PEP-related beliefs

To examine the association between knowledge of postexposure prophylaxis and perceptions on AIDS and safe sex, it was first necessary to determine whether respondents were aware of these prophylactic therapies. A 'gatekeeper' item was used for this purpose that described 'postexposure prophylaxis' as 'the opportunity for an HIV-negative individual to use antiretroviral therapy for a short period immediately after an unsafe sexual contact or condom failure in order to reduce the risk of HIV infection'. Respondents who answered 'no' to the question if they were aware of this opportunity, did not complete six items measuring PEP-related perceptions.

Again we used principal components analysis (PCA) with varimax rotation (assuming no correlation between the factors) to reduce the amount of data, to distinguish two principal components (Table II), each consisting of several related statements. The cumulative variance explained by the two components was 76.3%.

Reliability analysis was used to confirm internal consistency of scales constructed on the basis of identified principal components. The first principal component, *perceiving less HIV/AIDS threat since PEP availability,* explained 50.2% of the variance and consisted of four related statements with a reliability of 0.89. The second principal component, *perceiving high effectiveness of PEP in preventing HIV/AIDS,* explained 26.1% of the variance and consisted of two related statements with a reliability of 0.65.

Table II. Principal components of PEP-related beliefs and concerned statements identified among MSM-cohort in Rotterdam.

perceiving less HIV/AIDS threat since PEP availability (Cronbach's alpha: 0.89)
Since PEP is available, it is less important to use condoms
Unsafe sex is no longer a disaster since PEP is available
I am less afraid to get in touch with HIV since PEP is available
Since PEP is available, I am less afraid of HIV infection during sexual contact
perceiving high effectiveness of PEP in preventing HIV/AIDS (Cronbach's alpha: 0.65)
In case of an HIV risky sexual contact, PEP can prevent HIV infection
I think that PEP can eradicate the virus completely from your body if started right after infection with HIV

Venereological examination

At each biannual visit all participants underwent a standardised venereological examination as described previously. (19) In brief, blood samples were taken to test for HIV-antibodies, syphilis and hepatitis B. The examination also included testing for urethral, rectal and oropharyngeal gonorrhoea and urethral and rectal *Chlamydia trachomatis* infection.

Statistical Methods
Univariable and multivariable logistic regression analysis were used to investigate the association between HAART- and PEP-related beliefs and the incidence of STDs. A multivariable logistic regression model was built by including variables with an univariable p-value of less than 0.05. P-values were calculated using the likelihood ratio test. To investigate the association between HAART- and PEP-related beliefs and new HIV infection, only univariable and exact logistic regression were done because of the small numbers of new HIV cases.
All statistical analyses mentioned in this manuscript were done using SPSS for Windows, version 11.0, SPSS Inc., Chicago, USA. For exact logistic regression analysis LogXact-4 for Windows, version 4.1, Cytel Software Corporation, Cambridge, USA was used.

Results

Of the originally recruited 286 cohort participants, a total of 247 (86.4%) MSM completed the behavioural questionnaire with the statements concerning PEP and HAART at their third visit. The median age of these 247 MSM was 41 years (inter-quartile range 34 - 49), 93.2% were of native Dutch descent and 45.4% had high educational level. Ninety-one percent identified themselves as 'gay', and 9% described their sexual orientation as bisexual. The median number of sexual partners during the previous six months was 8 (inter-quartile range 3 - 20). With respect to HIV sero-status, 14 MSM (5.7%) were HIV-positive and 5 (35.7%) of these men were on antiretroviral therapy at their third visit.
Of the 247 MSM 80 (32.4%) indicated that they knew of PEP.

In total 151 HIV-negative MSM (52.8% of the original 286 cohort recruits), who participated in all five successive cohort visits, were included in this study. These MSM were comparable with all other MSM completing the self-administered questionnaire at the third visit with regard to median age, ethnicity, sexual orientation, number of sexual partners in the previous six months and educational level as well as incidence of STDs and HIV.
Of the 151 HIV-negative MSM, 99 (65.6%) tested negative for any STDs, including HIV infection, at all subsequent visits. Nine (6.0%) MSM had an STD twice or more often, and a total of 7 (4.6%) MSM HIV seroconverted during the study period.
Number and type of prevalent and incident STD and HIV infection detected at the consecutive cohort visits are summarised in Table III.

HAART-related beliefs
Of all MSM, between 4.0 and 32.7% (strongly) agreed with statements in principal component 1 of the HAART-related beliefs. Between 9.0 and 17.3% (strongly) disagreed with statements in principal component 3. These proportions for agreement with statements in principal component 4 were between 4.6 and 5.8%. A rather small minority of men (strongly) agreed with statements in principal component 2 (between 0.6 and 0.7%).

Table III. Number and type of incident STDs and HIV infection detected at the consecutive cohort visits.

cohort visit	NG urethral	NG rectal	NG oral	CT urethral	CT rectal	ES	HSV	HBV	HIV	total
3	0	2	0	3	4	0	0	4	3	16
4	2	2	2	6	4	0	0	1	2	19
5	0	5	0	4	5	2	0	4	1	21
6	1	5	0	2	3	0	1	0	1	13
7	1	1	1	3	0	1	0	1	0	8
total	4	15	3	18	16	3	1	10	7	77

NG denotes *Neisseria gonorrhoeae*, CT *Chlamydia trachomatis*, ES early syphilis, HSV genital herpes simplex virus, first episode and HBV (immune) hepatitis B virus infection

Table IV. Univariable and multivariable analyses of the association between HAART-and PEP-related beliefs, demographic data and *incidence of STDs* among HIV-negative MSM-cohort in Rotterdam.

	average scores		univariable analyses			multivariable analyses		
determinant	mean	SE	OR$	95% CI	p-value	OR@	95% CI	p-value
HAART-related beliefs								
perceiving less HIV/AIDS threat since HAART availability (average of 5 related statements)	2.17	0.16	1.42	(1.01-1.99)	0.041	1.71	(1.17-2.50)	0.005
perceiving less need for safe sex since HAART availability (average of 3 related statements)	1.13	0.052	1.70	(0.64-4.48)	0.29			
general beliefs concerning the start of HAART (average of 4 related statements)	3.74	0.12	0.68	(0.46-1.02)	0.058	0.76	(0.50-1.16)	0.20
perceiving high effectiveness of HAART in curing HIV/AIDS (average of 2 related statements)	1.70	0.13	1.00	(0.68-1.47)	0.98			
PEP-related beliefs								
perceiving less HIV/AIDS threat since PEP availability (average of 4 related statements)	1.37	0.16	1.23	(0.54-2.77)	0.63			
perceiving high effectiveness of PEP in preventing HIV/AIDS (average of 2 related statements)	2.71	0.20	0.98	(0.55-1.75)	0.94			
age (median, IQR, in years)	38.0	(31.0-43.0)	0.94	(0.90-0.98)	0.001	0.93	(0.89-0.97)	< 0.0005
educational level (N, % of total)								
low	4/16	25.0%	1					
middle	21/62	33.9%	1.54	(0.44-5.35)	0.78 #			
high	22/71	31.0%	1.35	(0.39-4.65)				
ethnicity (N, % of total)								
Dutch	42/140	30.0%	0.34	(0.09-1.34)	0.12			
non-Dutch	5/9	55.6%	1					
sexual partners previous 6 months (median, IQR, N)	10	(4-20)	0.99	(0.97-1.01)	0.23			

SE denotes standard error, OR odds ratio, CI confidence interval, IQR inter-quartile range and N number
$ the odds ratios per unit increase of the average score, ranging from 1 to 5
@ the odds ratios were adjusted for age
# overall p-value

Table V. Univariable analyses of the association between HAART-and PEP-related beliefs, demographic data and *incidence of new HIV infection* among HIV-negative MSM-cohort in Rotterdam.

	average scores		univariable analyses		
determinant	mean	SE	OR$	95% CI	p-value
HAART-related beliefs					
perceiving less HIV/AIDS threat since HAART availability (average of 5 related statements)	1.96	0.30	1.11	(0.52-2.34)	0.80
perceiving less need for safe sex since HAART availability (average of 3 related statements)	1.80	0.65	3.22	(1.27-8.16)	0.014
general beliefs concerning the start of HAART (average of 4 related statements)	3.50	0.45	0.56	(0.24-1.28)	0.17
perceiving high effectiveness of HAART in curing HIV/AIDS (average of 2 related statements)	1.75	0.28	1.01	(0.42-2.43)	0.99
PEP-related beliefs					
perceiving less HIV/AIDS threat since PEP availability (average of 4 related statements)	1.70	0.67	1.97	(0.51-7.65)	0.37
perceiving high effectiveness of PEP in preventing HIV/AIDS (average of 2 related statements)	2.50	0.50	0.71	(0.20-2.52)	0.60
age (median, IQR, in years)	41.0	(35.0-43.0)	0.97	(0.90-1.05)	0.40
educational level (N, % of total)					
low	0/17	0	NE		
middle	2/54	3.7%	NE		
high	5/65	7.7%	NE		
ethnicity (N, % of total)					
Dutch	6/136	4.4%	0.77	(0.24-15.88)	0.76
non-Dutch	1/7	14.3%	1		
sexual partners previous 6 months (median, IQR, N)	10	(5-20)	1.00	(0.95-1.03)	1.00

SE denotes standard error, OR odds ratio, CI confidence interval, IQR inter-quartile range, NE not estimable and N number
$ the odds ratios per unit increase of the average score, ranging from 1 to 5

In univariable analyses (Table IV), only one treatment-related belief component (*perceiving less HIV/AIDS threat since HAART availability*) and age were associated with the incidence of STDs. Men who reported less perceived HIV/AIDS threat were more likely to have an STD. Furthermore, older men were less likely to present with an STD. In multivariable analysis both variables remained independently associated with the incidence of STDs. Extending the model with the non-significant variables educational level, ethnicity and number of sex partners in the previous six months neither had any significant influence, nor did it change the already estimated coefficient and its significance.
With regard to new HIV infections (Table V), univariable analysis showed that the treatment belief factor *perceiving less need for safe sex since HAART availability* was associated with HIV seroconversion. Men who perceived less need for safe sex since HAART availability, were more likely to HIV seroconvert.

PEP-related beliefs
Of all MSM, between 1.6 and 1.7% (strongly) agreed with statements in principal component 1 and between 9.4 and 30.8% (strongly) agreed with statements in principal component 2 of the PEP-related beliefs.
There were no associations between any PEP-related beliefs and the incidence of STDs or new HIV infection.

Discussion

To our knowledge, this is the first study in which the relationship between the incidence of STDs and HIV infection, and HAART- and PEP-related beliefs in MSM was investigated. In this study we focused on the incidence of STD and HIV diagnoses rather than on self-reported unprotected anal intercourse. Longitudinal data that relate new STD and HIV infections to HAART and PEP-related perceptions contributes to our understanding of the extensively debated issue regarding the existence of any association between so-called 'HIV optimism' and risky sexual behavior in HIV-negative MSM.

In general, MSM in this Rotterdam cohort study were quite realistic about the effectiveness and consequences of HAART and PEP. This has also been reported in other studies. (7,17,8). The majority (86.2%) of MSM (strongly) disagreed with belief statements measuring less perceived threat of HIV/AIDS and (strongly) disagreed with the idea that safe sex was less necessary because of the availability of HAART (97.3%) or PEP (90.2%). Only a minority (4.2%) of MSM in our study (strongly) held the belief that new HIV/AIDS treatments can eradicate the virus from a person's body.
Nonetheless, the results of this study are consistent with the hypothesis that perceiving less HIV/AIDS threat since HAART is associated with more risky sexual behavior, which in turn might lead to a higher incidence of STDs in MSM. Perceived less need for safe sex was associated with HIV seroconversion. Although an association between 'perceiving less HIV/AIDS threat since HAART availability' and the incidence of STD was seen, no such an

association could be found between 'perceiving less need for safe sex since HAART availability' and the incidence of STDs. Possibly due to social desirability, some MSM were unwilling to report a tendency towards unsafe sex when participating in our cohort study.

Alternatively, one could assume that 'HIV-optimistic' men predominantly participate in sexual networks with a high prevalence of STDs and HIV infection. This seems, however, highly unlikely.
In their Chicago study, Vanable et al. noted a substantial minority of men who reported reduced HIV concern related to treatment advances. Despite the low prevalence of reduced concern, these authors warned that even slightly reduced concern could be associated with a considerable increase in the rate of HIV transmission.(8) It is hard to comment on a possible association between PEP-related beliefs and the incidence of STDs and HIV infection, since there was only limited awareness on the availability of PEP in our study.
It is important to be aware that our cohort consisted of MSM from the Rotterdam region who were invited to participate in the study, and therefore possibly were not representative of the MSM population at large neither in Rotterdam, nor in The Netherlands. The cohort of MSM primarily consisted of native Dutch, HIV-negative men in their forties, with high educational level. Extrapolation of our findings to the total population of MSM should therefore be done with caution.

Despite these limitations, the results of this study have implications for preventive interventions. Even a small minority of HIV-positive MSM who practice unsafe sex may increase the incidence of HIV infection. Reduction in risky sexual behavior therefore needs continued emphasis. The advice on the use of condoms during anal sex is important in the light of (long-term) side effects of HAART and PEP, recent increase in the incidence of HIV infection world-wide and increasing transmission of drug-resistant HIV-1 strains.(17,21,22) Such advice should also include the fact that, whereas treatment progress has been made, there is still no cure for HIV and that some patients are non-responsive to antiretroviral therapies. Finally, it is necessary to stress the fact that an undetectable viral load does not eliminate the risk of infection.(8) Discussing these issues including participants perceptions on HAART is necessary in consultations with either medical specialist or paramedical staff in contact with the patient.

In conclusion, the results of this study showed that, in general, MSM participating in our cohort were realistic on their beliefs on the effectiveness of HAART and PEP. The large majority of participants did not find safe sex less necessary because of the availability of HAART and PEP. Nevertheless, the reported findings are consistent with the hypothesis that a decreased perception of HIV/AIDS threat because of HAART availability, might lead to increasing incidence of STD and HIV infections. Therefore, ongoing prevention emphasis on reducing risky sexual behavior by using condoms during anal sex is essential.

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chapter 8

Incidence of STDs and HIV infection in men who have sex with men related to knowledge, perceived susceptibility and perceived severity of STDs and HIV infection: Dutch MSM-cohort study

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Abstract

Background: This longitudinal study was conducted to investigate whether knowledge, perceived susceptibility and perceived severity of HIV infection and STDs, are associated with incidence of STDs and new HIV infections among MSM.

Methods: A three-year cohort study was conducted among 276 HIV-negative MSM. Data were collected on the incidence of STDs and new HIV infections, as well as on knowledge, and perceived susceptibility to and perceived severity of HIV infection and STDs. Knowledge and perceptions were assessed in self-administered questionnaires.

Results: In the course of the three-year study, 14 MSM (5.1%) HIV-seroconverted and forty percent of participant were diagnosed with at least one STD. MSM seemed to be better informed about HIV infection compared to STDs, and HIV infection was perceived as more severe than other STDs.
In multivariable analyses, the practice of anal intercourse was associated with an increased risk of acquiring an STD ($p = 0.038$), and low perceived severity of HIV infection (marginally) significantly ($p = 0.053$) predicted increased likelihood of infection with STDs. Higher numbers of sex partners were associated with an increased risk of acquiring HIV infection ($p = 0.006$).

Conclusions: A high perceived severity of HIV infection seems to induce sexual behaviour which protects against STDs. We did not find a relation between perceived severity of STDs and incidence of HIV infection. More research is needed to establish the process by which perceived severity of HIV influences sexual behaviour and incidence of STDs.

Introduction

In recent years, substantial increases in diagnosed infections with gonorrhoea and early syphilis among men who have sex with men (MSM) have been reported from numerous cities around the world, including San Francisco, London, Sydney and Amsterdam.[1-5] Some recent studies from San Francisco, Ontario and Amsterdam also found increasing HIV infection rates among MSM.[6-8]
Increasing numbers of infections with STD and HIV are taken to indicate higher levels of sexual risk behaviour among MSM for which different explanations have been suggested. Major hypotheses put forward in the literature explain higher levels of sexual risk-taking among MSM as a result of one or more of several factors: optimism due to highly active antiretroviral therapy (HAART), HIV-prevention-fatigue (i.e. MSM became habituated to the risk of HIV infection after two decades of AIDS); increased sex seeking on the internet and an increased opportunity for meeting sexual partners in saunas and backrooms.[9-20]

While seemingly disparate, these alternative explanations may at least in part have a common pathway that results in increased sexual risk behaviour in MSM. Research testing the optimism explanation of increased risk-taking in particular has found that among MSM perceptions of the health threat posed by HIV have decreased, as has the need for protective sexual behaviour.[9-11] These changed perceptions and motivations predict an increase of unprotected anal sex with casual partners and infection with STD and HIV among HIV-negative MSM.[16,18] Reduced perceptions of threat and need for protection are also likely to result from HIV-prevention fatigue, and can equally explain why men engage in sexual risk-taking with partners they met through the internet or sex-on-premises venues.
Studies assessing the role of perceptions as mediators of increased risk-taking among MSM thus far have measured a diverse range of potentially relevant perceptions, only some of which seem to be related to behaviour change.[16] A drawback of existing research is that the diversity of measures of perceptions makes any comparison of different studies virtually impossible. Also, in most studies no apparent theoretical framework is used to derive predictors or explain the pattern of findings, which limits any real appreciation of the importance of reported predictors of increased risk-taking among MSM and hinders translation of findings into health promotion programs that generally are based on behaviour change theories and related intervention strategies. Also, studies generally rely on self-reported risk behaviours as outcome variable. As far as we are aware, only one recent study related perceptions of HIV-related health threat to biological markers of risk-taking (i.e. infection with HIV or STDs).[18] The purpose of the present study is to provide a theoretical framework from which pertinent perceptions of health threat that may explain sexual risk behaviour among MSM can meaningfully be derived, and to assess the empirical relevance of these theory-based determinants as predictors of incidence of HIV and STDs among MSM.
A number of widely used social-psychological theories of behaviour change are available that identify theory-based correlates of readiness to engage in certain behaviours, including sexual risk behaviours.[21] These theories have in common that they specify a limited number of social-

cognitive factors that explain behaviour, but differ in the types of factors they specify, the way factors are thought to interrelate and explain behaviours, as well as the categories of behaviours the theories attempt to explain. Theories of health behaviour, such as the health belief model, and the largely similar protection motivation theory, assume that an individual must experience a sense of personal health threat before protective action will be initiated.[22-25] Although the health belief model does not address this explicitly, it is likely that when the perceived health threat subsides, the motivation to engage in protective behaviour will equally diminish.

The health belief model provides an understanding of some of the beliefs that determine safe sex adoption and has contributed to the development of intervention efforts designed to increase safe sex among MSM, as have other social-cognitive behaviour theories that consider wider classes of behaviour, notably social cognitive theory, the theory of reasoned action, and the theory of planned behaviour.[26-30] The health belief model is particularly relevant to the current study of sexual risk-taking because it specifies perceived health threat as a necessary condition for behaviour change, which matches the findings from a recent study that has demonstrated that reduced perceived threat of HIV results in uptake of unprotected anal sex among MSM.[16] According to the health belief model, perceived health threat results from two specific perceptions: perceived susceptibility to the illness or condition, and perceived severity of the illness/condition. Among MSM both perceived susceptibility to HIV infection and perceived severity of infection most likely have diminished in recent years.[31]

This study investigated the relevance of core aspects of the health belief model in understanding potential consequences of unprotected anal intercourse, in a cohort of MSM in Rotterdam, the Netherlands. In particular, we studied whether, among MSM, perceived susceptibility to STDs and HIV infection and perceived severity of infection with HIV and STDs were associated with the incidence of HIV infection and STDs, respectively. In addition, we studied whether knowledge of HIV infection and STDs contributed to the prediction of incidence. An additional question concerned whether a high perceived threat of becoming infected with STDs could induce sexual behaviour that also protects against HIV infection, as reflected in a lower HIV-incidence in MSM with higher perceived susceptibility and severity of STDs. The aim of this study was to contribute information that can be used in health promotion programs that support MSM in achieving a reduction in sexual risk behaviour.

Materials and Methods

Study population and study design

The study was conducted at the STD clinic of the Department of Dermatology and Venereology, Erasmus University Medical Centre Rotterdam, the Netherlands.
Beginning in February of 1999, we recruited 286 MSM to participate in the Rotterdam MSM-cohort study. Both HIV-positive and HIV-negative MSM were recruited by trained volunteers at gay meeting places like bars and saunas. The way participants were recruited has been described in more detail elsewhere.[32] At enrolment all participants provided written informed

consent. The ethics committee of our hospital approved the protocol. Cohort participants were tested for STDs and HIV every six months. In case of STD symptoms in between two biannual cohort visits, participants were urged to visit the STD clinic at short notice. Inclusion criteria for the present study were: having had sex with at least one male partner in the preceding twelve months, being HIV-negative at enrolment and having participated in at least five of six successive cohort visits. Those MSM who never had an STD, did not HIV seroconvert during the three-year cohort study, but did not attend all six visits were excluded from the analyses. These men could not definitely be considered STD-negative throughout the study period, because of the missing of one cohort visit. For the remaining STD-negative participants spontaneous clearance of any asymptomatic STD during the sixth-months intervals can not be ruled out completely.

Data collection and questionnaires

At each visit medical history was taken, including self-reported information on STDs in the past 6 months. Also, demographic and sexual behaviour information was collected including ethnic background, age, educational level (defined as 'low' with school attendance up to the age of about 16 years, 'middle' with school attendance up to the age of about 18 years, or 'high' indicated by a college degree or equivalent), sexual orientation, number of sexual partners during the previous six months and having engaged in anal sex in the preceding six months. Participants further completed self-administered questionnaires on potential psychosocial predictors, including knowledge, perceived susceptibility and perceived severity of HIV infection and STDs. All measures were newly developed for this study.

Perceived susceptibility

To examine individuals' perceived susceptibility to sexual acquisition of different STDs, including HIV, we used a total of 160 items that were scored on six-point rating scales (1 = 'absolutely impossible'; 6 = 'extremely high'), and an additional 'don't know' option. Assessment of the perceived likelihood of an infection related to sexual behaviour was examined using the format 'What do you think is the risk of becoming infected with 'X' as a consequence of ?' followed by a specific sexual act.

At the first and fourth visit 40 items were included that measured perceived susceptibility to HIV, condylomata acuminata, genital herpes, and hepatitis A and B. At the second and fifth visit 40 items were included on perceived susceptibility to HIV, gonorrhoea, chlamydia, and hepatitis B. Participants were asked to self-report their perceived susceptibility to acquisition of these infections as a result of different sexual acts. A perceived susceptibility scale was constructed by averaging scores across all items ('don't know' responses were not counted).

Perceived severity

To examine individuals' perceived severity of them personally acquiring different STDs, including HIV, we used a total of 42 items that were scored on four-point rating scales (1 = 'absolutely not severe'; 4 = 'extremely severe'), including a 'don't know' option. The perceived

severity of an infection was examined using the format 'How severe would you find if you were infected with …. (e.g. HIV, gonorrhoea, chlamydia?)'.
At all visits 7 items were included that measured perceived severity of HIV, syphilis, hepatitis B-infection, gonorrhoea, chlamydia, condylomata acuminata and genital herpes. A perceived severity scale was constructed by averaging scores across items ('don't know' responses were not counted).

Statements concerning knowledge of STDs and HIV infection (#) used at the first, second, fourth and fifth visit of the Rotterdam MSM-cohort

After one sex contact someone can be infected with HIV (#)
Lubricants on oil basis increase the vulnerability of condoms
Male precome can contain HIV-particles (#)
Receptive anal intercourse without intra-anal ejaculation is safe for HIV infection (#)
Anal intercourse without condom is unsafe for HIV infection (#)
Blood and sperm contains more HIV-particles than any other bodily fluid (#)
Oral-anal sexual contact ('rimming') can cause an hepatitis A-infection
A tonsillar gonococcal infection can only happen after oral sex with ejaculation
Chlamydial infections at the anus do only occur after unprotected anal intercourse
Hepatitis B-infection can not be transmitted sexually
Digito-anal sex can not transmit an STD
A chlamydial infection will eventually be symptomatic
Scabies is not sexually transmitted
Non-penetrable contact between penis and anus is safe for HIV (#)
Non-penetrable contact between penis and anus can not transmit an STD
Hepatitis B-infection can be prevented by vaccination
Syphilis almost never occurs in the Netherlands these days
When a person has the clap (gonococcal infection), it is very unlikely that this person has another STD at the same time

Knowledge of STDs and HIV
At the first, second, fourth and fifth visit eighteen recurrent true/false/don't know items assessed participants' STD (12 items) and HIV knowledge (6 items). These items comprised statements about HIV, chlamydia, gonorrhoea, syphilis, and hepatitis A and B. We used statements like: 'Receptive anal intercourse without intra-anal ejaculation is safe for HIV infection', 'oral-anal sexual contact ('rimming') can cause an hepatitis A-infection'; 'Chlamydial infections at the anus do only occur after unprotected anal intercourse'.

At the third and sixth visit another 10 true/false/don't know items assessed STD knowledge only. These items comprised questions about genital herpes, condylomata acuminata, and again, chlamydia, gonorrhoea, syphilis, and hepatitis A.
A scale was constructed from these items by counting each participant's correct responses ('don't know' responses were counted as incorrect).

Statements concerning knowledge of STD used at the third and sixth visit of the Rotterdam MSM-cohort

Passive oral sex by a person with a cold sore can cause genital herpes
A gonococcal infection at the anus almost always causes symptoms
A chlamydial infection can occur at the eyes
Early syphilis gives a painless ulcer at the penis, around the anus or in the throat
Vaccination for hepatitis B-infection is only possible when a person has never been infected with hepatitis B before
Vaccination for hepatitis A-infection does not exist
Genital warts do not occur very often these days
If ever infected with genital warts, a person always stays contagious
Adequate condom use does always protect against genital warts
Genital herpes infection can cause symptoms at the anus

Venereological examination
At each biannual visit all participants underwent a standardised venereological examination as described previously.[32] In summary, blood samples were taken to be tested for HIV-antibodies, syphilis and hepatitis B. The examination also included testing for urethral, rectal and oropharyngeal gonorrhoea and urethral and rectal *Chlamydia trachomatis* infection. Genital herpes simplex virus infections and symptomatic human papillomavirus infections (condylomata acuminata) were excluded from this study because in most cases we could not be sure whether these were prevalent or incident. Prevalence, persistence and acquisition of human papillomavirus infections in this MSM-cohort have been described before.[33,34]

Statistical methods
Participants with and without HIV and with or without STDs were compared to assess differences in knowledge, perceived susceptibility and perceived severity of HIV infection and STDs. A multivariable logistic regression model was built by including all variables with an univariable p-value of less than 0.20. P-values were calculated using the likelihood ratio test. The univariable association between knowledge, perceived susceptibility and perceived severity of HIV infection and STDs and demographic characteristics as well as sexual behaviour was analysed using the Spearman rank correlation test.

For men who only participated in five cohort visits and consequently had missing values, total scores for knowledge, perceived susceptibility and perceived severity were calculated as the average of the available scores.

Results

Demographic characteristics and sexual behaviour

Between February 1999 and February 2000 a total of 286 MSM were included in the cohort study, with a median age of 39.5 (range 18 - 75; IQR 33 - 48). Of all included participants 266 (93.0%) were of Dutch descent. The educational level of 122 participants (42.7%) was 'high', and 'middle' for 127 participants (44.4%). Characteristics of the study sample and epidemiological as well as behavioural parameters as obtained at first visit have been described previously.[35]

At entry into the study 251 MSM (87.8%) stated to be exclusively homosexual. The median number of sex partners in the six months preceding the first visit was 7 (range 0-130). In that period anal sex had been practised by 183 men (64.0%), while 58 men (20.3%) stated to never have had anal sexual intercourse.

An earlier diagnosis of STD was reported by 181 MSM (63.3%). Only 1 person (0.3%) worked as a male prostitute in the previous 6 months, and only 11 MSM (3.8%) declared to have had sex with a male prostitute in the previous 6 months. None of the participants had used any drugs intravenously.

In total 200 MSM (69.9% of the original 286 cohort recruits), completed the questionnaire at the sixth cohort visit. These MSM did not differ significantly from the full sample of original cohort recruits in median age, ethnicity, educational level, sexual orientation, number of sexual partners, practising anal sex and history of STDs.

STD/HIV prevalence

Table I summarises the incidence of STD and HIV infection (new diagnoses) in study participants and the number of participants tested during all six consecutive visits. Only the first visit includes prevalent STDs and HIV infections. All participants who were, at the first visit, diagnosed with an immune status after hepatitis B infection, were unaware of this.

One hundred fifteen MSM (40.2%) were diagnosed with an STD during at least one of the six visits. A total of 110 MSM (38.5%) who participated in all six successive cohort visits were never diagnosed with an STD. The remaining 61 MSM (21.3%) had no STD but did not participate in all visits.

Chlamydial infections were most often detected. Early syphilis was seen in only five MSM.

At their first study visit 10 men (3.5%) were known to be HIV-positive. During the three-year cohort follow-up an additional 14 of the remaining 276 MSM (5.1%) HIV seroconverted. One seroconverter was not eligible for this study because he did attend less than five cohort visits. Twelve of 13 seroconverters (92.3%) who were eligible for this study were diagnosed with an STD during at least one of the cohort visits, compared to 77 (41.6%) of 185 MSM who remained HIV-negative ($p < 0.001$). Five of 13 eligible seroconverters (38.5%) had a concomitant STD during the visit at which HIV seroconversion was detected. Most often this

concerned rectal gonorrhoea and rectal chlamydial infection. No early syphilis was seen in the MSM who serocenverted during the cohort study. Five of 13 eligible seroconverters had an STD at least one year before their seroconversion. One seroconverter was diagnosed with a rectal gonorrhoea two years after HIV seroconversion.

Table I. Number of individuals with incident STDs and HIV infection detected at six consecutive study visits in a cohort of MSM in Rotterdam (first visit includes prevalent STDs and HIV infection).

cohort visit	1	2	3	4	5	6	total
	n = 286	n = 271	n = 257	n = 243	n = 226	n = 211	n = 1494
NG	10	6	5	7	7	6	41
CT	23	21	8	10	7	9	78
ES	1	0	0	0	3	1	5
HBV	38	1	4	1	5	0	49
HIV	4	2	3	3	1	1	14
total	76	30	20	21	23	17	187

NG denotes *Neisseria gonorrhoeae*, CT *Chlamydia trachomatis*, ES early syphilis, and HBV (immune) hepatitis B virus infection

Knowledge, perceived susceptibility and perceived severity

Knowledge of HIV infection was measured in 250 MSM who on average scored 80% correct answers (range 21 - 100%). The 225 MSM among whom knowledge of STDs could be assessed on average answered 61% of the questions correctly (range 7 - 96%). MSM in this study were significantly better informed about HIV infection compared to STDs ($p < 0.0005$).
Two-hundred forty-four MSM completed items measuring perceived susceptibility to HIV. Mean perceived susceptibility to HIV was 3.9 (range 1.9 - 5.5). Perceived susceptibility to STDs could be assessed in 232 MSM. Mean perceived susceptibility to STD also was 3.9 (range 0.9 - 5.8).
Measurement of perceived severity of HIV infection is based on two-hundred twenty-two MSM who completed relevant items. Mean perceived severity of HIV was 3.9 (range 1.8 - 4) indicating that most participants had a very high perceived severity regarding HIV.
Two-hundred thirteen MSM completed the items concerning the perceived severity of STDs. Mean perceived severity of STDs was 2.9 (range 0.5 - 4). In general, participants perceived STDs as significantly less severe than HIV infections ($p = 0.0005$).

Table II. Univariable associations between incidence of STDs and HIV infection and knowledge, perceived susceptibility and perceived severity of HIV infection and STDs in a cohort of MSM in Rotterdam.

	individuals with STD infection(s)			individuals with HIV infection		
	OR	95% CI	p-value	OR	95% CI	p-value
perceived severity of HIV infection	0.80	0.64 – 1.00	0.038	0.80	0.58 – 1.10	0.23
perceived severity of STDs	1.00	0.99 – 1.01	0.66	0.98	0.95 – 1.01	0.12
perceived susceptibility to HIV infection	0.99	0.98 – 1.01	0.51	0.99	0.95 – 1.02	0.43
perceived susceptibility to STDs	1.00	1.00 – 1.00	0.63	1.00	1.00 – 1.01	0.58
knowledge about HIV infection	0.90	0.83 – 0.98	0.016	0.86	0.72 – 1.02	0.092
knowledge about STDs	1.00	0.97 – 1.02	0.80	1.00	0.94 – 1.07	0.97
anal sex in last six months	2.45	1.38 – 4.34	0.002	3.65	0.80 – 16.71	0.058
increasing number of sex partners by 10	1.14	0.90 – 1.31	0.065	1.22	1.03 – 1.44	0.041
having (had) an STD	-			16.82	2.14 -132.06	< 0.0005
having an HIV infection	16.83	2.1 –132.14	< 0.0005	-		

OR denotes odds ratio, CI confidence interval

Univariable analyses were performed to assess the association between demographic characteristics and sexual behavioural and knowledge, perceived susceptibility and perceived severity of HIV infection and STDs (Table II). Knowledge of HIV infection was significantly related to age ($p = 0.034$). Older participants reported less knowledge of HIV infection. Having had an STD in the past was related to knowledge of STDs ($p = 0.039$). Individuals who had had one or more STDs in the past were more knowledgeable about STDs. Educational achievement was associated with knowledge of both HIV infection ($p = 0.001$) and STDs ($p < 0.0005$). Higher educated men had more knowledge of HIV and STDs. Ethnicity ($p = 0.024$). and having had an STD in the past ($p = 0.004$) were associated with perceived susceptibility to STDs. Non-Dutch participants found themselves less susceptible, while individuals who had had one or more STDs in the past perceived themselves to be more susceptible to STDs.
Age ($p = 0.008$) was significantly related to perceived severity of HIV infection. Older participants reported lower perceived severity of HIV infection. Educational achievement was significantly related to perceived severity of STDs. Higher educated men reported lower perceived severity of STDs.
Sexual orientation (homosexual versus bisexual), number of sex partners and the practice of anal sex in the preceding 6 months were not associated with knowledge, perceived susceptibility to and perceived severity of HIV infection and STDs.

Table III. Univariable associations between demographic characteristics and sexual behaviour and knowledge, perceived susceptibility and perceived severity of HIV infection and STDs in a cohort of MSM in Rotterdam.

	homosexual orientation	increasing age	non-Dutch ethnicity	higher educational qualification	increasing number of sexual partners	increasing number of STDs in past	anal sex during last 6 months
perceived severity of HIV infection	0.81	0.008 R_s = -0.18	0.15	0.85	0.12	0.32	0.81
perceived severity of STDs	0.28	0.29	0.26	0.049 R_s = -0.14	0.15	0.091	0.46
perceived susceptibility to HIV infection	0.26	0.16	0.12	0.57	0.099	0.70	0.45
perceived susceptibility to STDs	0.11	0.60	0.024 R_s = -0.15	0.55	0.63	0.004 R_s = 0.19	0.48
knowledge about HIV infection	0.33	0.034 R_s = -0.14	0.33	0.001 R_s = 0.21	0.85	0.14	0.16
knowledge about STDs	0.48	0.69	0.12	< 0.0005 R_s = 0.26	0.48	0.039 R_s = 0.14	0.10

p-values are Spearman p-values; R_s denotes correlation coefficient Spearman test

Explaining infection with HIV and STDs

Univariable analyses (Table III), showed that time of occurrence of HIV infection and STDs were significantly correlated (OR = 16.83; $p < 0.0005$), indicating that HIV infection and STDs were likely to co-occur. Furthermore, knowledge of HIV infection and perceived severity of HIV infection were associated with being diagnosed with at least one or more STDs. MSM who had less knowledge of HIV infection (OR = 1.11; $p = 0.016$), as well as MSM who indicated lower perceived severity of HIV infection (OR = 1.25; $p = 0.038$), had a higher likelihood of having had an STD.

Anal intercourse in the last six months was also significantly correlated (OR = 2.45; $p < 0.002$) with being diagnosed with at least one or more STDs. Furthermore, MSM who had sexual contact with more partners (OR = 1.22; $p = 0.041$), had a higher likelihood of acquiring an HIV infection. No other univariable relations between infection with HIV or STDs and measures of knowledge, perceived susceptibility and perceived severity were found at conventional levels of statistical significance ($p < 0.05$).

Table IV. Multivariable associations between incidence of STDs and HIV infection and demographic characteristics and sexual behaviour and knowledge, perceived susceptibility, perceived severity of HIV infection and STDs in a cohort of MSM in Rotterdam.

	individuals with STD infection(s)			individuals with HIV infection		
	OR	95% CI	p-value	OR	95% CI	p-value
perceived severity of HIV infection	0.80	0.63 – 1.02	0.053	-		
perceived severity of STDs	-			0.98	0.95 – 1.01	0.25
knowledge about HIV infection	0.95	0.84 – 1.06	0.36	0.86	0.61 – 1.20	0.37
increasing age	1.00	0.97 – 1.04	0.97	0.94	0.86 – 1.04	0.24
non-Dutch ethnicity	0.42	0.09 – 1.96	0.26	-		
higher educational qualification	0.83	0.49 – 1.39	0.47	3.46	0.55–21.85	0.17
increasing number of sex partners by 10	1.11	0.90 – 1.34	0.24	1.49	1.11 – 2.00	0.006
anal sex in last six months	2.06	1.03 – 4.10	0.038	0.74	0.05 – 9.96	0.82
increasing numbers of STDs	1.10	0.86 – 1.42	0.44	1.07	0.61 – 1.86	0.82
having an STD	-			4.82	0.40–58.52	0.18
having an HIV infection	NE			-		

OR denotes odds ratio, CI confidence interval, NE not estimable

In multivariable analyses all predictor variables were entered that univariably were related to infection with HIV or STD at $p < 0.20$ (table IV). Analyses showed that having had one or more STDs was significantly associated with having engaged in anal intercourse in the preceding six months (OR: 2.06; $p = 0.038$). In addition, a (marginally) significant effect was found for perceived severity of HIV infection (OR: 0.80; $p = 0.053$). Lower perceived severity of HIV infection increased the likelihood of HIV infection. Number of sex partners was related to HIV seroconversion (OR: 1,49; $p = 0.006$). Men who reported higher numbers of sex partners were more likely to have HIV seroconverted.

Discussion

This study investigated whether, among MSM in Rotterdam, perceived susceptibility to STDs and HIV infection and perceived severity of infection with STDs and HIV, as well as knowledge of STDs and HIV infection were associated with the incidence of STDs and HIV infection, respectively. An additional question concerned whether a high perceived threat of becoming infected with STDs could induce sexual behaviour that also 'protects' against HIV

infection, as reflected in a lower HIV-incidence in MSM with higher perceived susceptibility and severity of STDs.

Men who were diagnosed with an STD at one or more of the cohort visits were significantly more likely to become infected with HIV than men who did not have an STD. Almost 40% of the MSM who HIV seroconverted had a concomitant STD at the time when HIV seroconversion was detected. Multivariable analyses showed that risk of acquiring an STD was higher in MSM who practised anal intercourse. Higher numbers of sex partners significantly increased the likelihood of HIV seroconversion. High perceived severity of HIV infection marginally significantly decreased the likelihood of infection with STDs. Perceived susceptibility to STDs and HIV infection was not found to be related to either infection with STDs or HIV, nor was knowledge of STDs and HIV infection.

Practising anal intercourse increased MSMs risk for infection with STDs, which presumably indicates a relation between risky practices and likelihood of infection. Unfortunately, in this study insufficient data were available regarding participants' condom use to further test this reasoning. Nevertheless, we do know that between 20 and 30% of the MSM did not consequently use condoms while having anal sex, and avoiding or modifying unprotected receptive anal sex has also been identified as a behaviour that significantly reduces the risk of HIV infection.[36-40] Contrary to our explanation that the relation between practising anal sex and infection with STD reflects risk-taking, in this study no association between the practice of anal intercourse and the risk of HIV infection could be found. This, however, is most likely due to the low number of HIV seroconversions.

The association between numbers of sex partners and risk for HIV infection that was obtained in this study has been observed before. Notably, in the early stages of the HIV epidemic, reducing one's number of sexual partners was found to reduce the risk of HIV seroconversation.[41] Recently, a national survey among MSM in the Netherlands equally observed an association between higher numbers of sexual partners and an increased likelihood of infection with STDs.[42] This association might reflect a higher likelihood of engaging in unprotected anal sex with increasing numbers of partners.

It is of interest to find that a high perceived severity of HIV infection (marginally) significantly decreased the likelihood of infection with STDs. This indicates that MSM with higher perceived threat of HIV may differ in their sexual behaviour in ways that reduces their likelihood of infection with STD. Additional analyses showed that MSM with higher perceived threat of HIV are significantly younger than MSM with lower perceived threat of HIV ($p = 0.013$). However, no differences could be found regarding number of sexual partners in the preceding 6 months or the practice of anal sexual intercourse ($p = 0.10$ and $p = 0.84$ respectively). The exact way in which perceived severity of HIV affects sexual behaviour presently remains unclear and more research is needed to establish how perceived severity of HIV influences both (sexual) behaviour and incidence of STDs.

In this study knowledge about STDs and HIV infection was not associated with the incidence of STDs or HIV infection. This is not in concordance with a recent study in St. Petersburg in which a significant association between knowledge of HIV/AIDS and attitudes toward

condom use was found. The authors of the St. Petersburg study concluded that there were substantial gaps in respondents' understanding of HIV transmission.[43] In Rotterdam, knowledge about STDs and especially HIV infection among cohort participants was rather high compared to the study in St. Petersburg. Increasing knowledge of the Rotterdam cohort participants will thus likely only have limited value in the prevention of new STDs and HIV seroconversion.
Perceived susceptibility to STDs and HIV infection does not seems to influence the incidence of STDs and HIV. This is in contrast with a recent study among MSM that investigated determinants of vaccination against hepatitis B and which found perceived susceptibility to be the most important predictor.[44] However, this latter study assessed protective behaviour while the present study focused on outcomes of risk-taking which may explain the disparate findings.

It is important to note that cohort participants constitute a convenience sample of MSM from the Rotterdam region, which possibly is not representative of any larger community of MSM, neither in the city of Rotterdam, nor in The Netherlands as a whole. This cohort primarily consisted of native Dutch, HIV-negative MSM in their forties, with a high educational level. Extrapolation of our findings to the larger population of MSM should therefore be done with caution. However, despite this limitation our findings do have importance. In particular, we found that a psychosocial variable, notably high perceived severity of HIV infection, was related to a lower likelihood of infection with STDs. Furthermore, contrary to expectations, the perceived threat of becoming infected with STDs did not have a similar effect on the likelihood of infection with HIV. To our knowledge, studies on the relation between perceptions of threat and incidence of STDs and HIV have not been published previously. Such studies may provide an important avenue for research that aims to contribute to an understanding of epidemiological trends. Due to limitations of the present study, the way perceived severity of HIV influences (sexual) behaviour that protects against infection with STDs remains to be studied in more detail. Such future research can provide important information regarding psychosocial processes that co-determine disease outcomes and can contribute to the development of health promotion programs that support MSM in achieving a reduction in sexual risk behaviour.

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chapter 9

general discussion

The (cumulative) incidence of STDs and HIV infection

Monitoring the (cumulative) incidence of STDs and HIV infection in MSM was one of the aims of the studies in this thesis. Despite increases in gonorrhoea and early syphilis in several cities, no such rise was seen in the Rotterdam cohort study apart from a slight increase of early syphilis in 2001 (Table 1). [1-6]

Table 1. Rotterdam cohort study.

std / year	1999 (1)	2000	2001
number of participants tested for HIV	557	500	437
known to be HIV-positive	23	28	26
HIV-seroconverts (2)	6	6	2
HIV incidence	1.1	1.3	0.5
number of participants tested for STDs	557	500	437
early syphilis (3)	1 (0.2)	0	4 (0.9)
gonococcal infections (4)	16 (2.9)	12 (2.4)	13 (3.0)
rectal infection	11	7	12
urethral infection	5	3	2
tonsillar infection	1	3	0
chlamydial infections (4)	44 (7.9)	18 (3.6)	16 (3.7)
rectal infection	27	10	10
urethral infection	24	9	10
HBV-immunity (anti-HBc-positivity) (5)	39	5	5

(1) includes prevalent STDs at the first visit
(2) at the first visit: previously tested negative or were never tested for HIV
(3) primary, secondary and early latent syphilis (VDRL ≥ 1:8)
(4) number of infected participants
(5) at the first visit: all participants who were not aware of their anti-HBc status were counted (includes prevalent HBV infections)

The incidence of HIV infection remained rather stable and was between 0.5 and 1.3. In 1999, chlamydial infections and hepatitis B infections with acquired immunity (HBV immunity) were seen very frequently. The high number of mostly asymptomatic chlamydial infections and HBV immunity in 1999 could be explained by the fact that some of these infections were present for a longer period and were therefore prevalent instead of being incidental cases. Only those participants diagnosed with HBV immunity at the first visit who were unaware of this are shown in Table 1. Of all participants only three MSM were HBsAg-positive at enrolment. All these men were aware of this. None of the incident hepatitis B infections in the cohort period were infectious for more than 6 months.
The incidence of the usually symptomatic gonococcal infections did not change over the years. In 2001, a slight increase in early syphilis was seen. Two out of the four cases were HIV-positive MSM.
A total of 110 (38.5%) MSM who participated in all six successive biannual cohort visits were never diagnosed with an STD. One-hundred-fifteen (40.2%) MSM were diagnosed with an STD during at least one of the six visits. All other 61 (21.3%) MSM had no STD but did not attend all visits.

Condom use
Why no increase could be detected in rectal gonorrhoea as well as early syphilis in the Rotterdam cohort study remains unknown. As was suggested in chapter 4, the MSM participating in the cohort may have been (very) cautious individuals and therefore less at risk of an STD. Maybe this group was less at risk for STDs or HIV infection because of the precautions they had taken.
According to the information from the self-administered questionnaires, 54.5% of all participants from the Rotterdam cohort study had anal sex with casual partners in the preceding six months. Of these MSM, 23.3% did not consequently use condoms during receptive anal sex. In case of insertive anal intercourse, 29.3% MSM stated that they did not always use condoms.
Concerning active oral sex, 10.0% of all cohort participants stated that they had active oral sex accompanied by intra-oral ejaculation with casual partners in the preceding six months. Of them, only 3 out of the 10 MSM consequently used condoms under these circumstances.
In 2002 and 2003, 100 MSM visiting the Rotterdam STD clinic were invited to complete a questionnaire with the same items as that was used in the Rotterdam cohort study. These STD clinic visitors were invited to complete the questionnaire at home and return it in a pre-paid envelope. The MSM were paid 15 Euro by the department of Dermatology and Venereology of the Erasmus MC as soon as the completed questionnaire had been received.
Of these MSM, 89 (89.0%) had had anal sex with men and 62/89 (69.7%) stated that they always used condoms. These data refer to all lifetime sexual encounters of all the MSM concerned. No data on oral sex and condom use were available in this group.
In both the national survey among MSM (Monitor study) in 2000 and 2003, 34% of all MSM having anal sex with casual partners stated that they did not always use condoms. Unprotected oral sex in 2000 was comparable with the results of the national survey in 2003. Thirteen

percent stated that one of more sexual partner(s) had ejaculated in their mouth during active oral sex in the preceding six months. When these percentages were compared with the data from the cohort study, we could conclude that MSM participating in the cohort used condoms during anal and oral sex with casual partners slightly more (Table 2).

Table 2. Sexual intercourse with casual partners in the preceding 6 months.

sexual act / group	Rotterdam cohort study	National survey 2000	National survey 2003
sex with casual partners	87%	74%	70%
median number of partners (range)	10 (1 - 140)	6 (1 - 540)	5 (1 - 400)
anal sex with casual partners	55%	50%	61%
no consequent condom use during anal sex[1]	23 / 29%[3]	33%	34%
unprotected oral sex with ejaculation[2]	7%	9%	13%

(1) of those who practised anal sex with casual partners during the preceding 6 months
(2) of those who had sex with casual partners during the preceding 6 months
(3) in receptive versus insertive anal sex

Another possible explanation may be low prevalences of STDs and HIV infection within a rather consistent highly active sexual network. This may explain the low cumulative incidence of STDs diagnosed in our group. However, we have no reason to believe that this is the case in the Rotterdam cohort.

The STD clinic in Rotterdam
The STD clinic of the Erasmus MC is the main facility in Rotterdam where one can be tested for STD. Only the STD clinic in Amsterdam has more visitors every year. Persons with STD-related symptoms or risky sexual behaviour may be tested free of charge without being referred by a general practitioner. Demographic and STD/HIV data are recorded comparable with the standard procedures in the Rotterdam cohort study.
A definite increase in the number of MSM visitors was seen from 1999 to 2001 (Table 3). There was a remarkable rise in the number of MSM tested in 2001. In that year an increase in early syphilis and urethral gonorrhoea was seen. This increase was comparable with the data of MSM communities in Amsterdam and elsewhere.[5,7] Chlamydial infections or HIV infections did not show such an increase.

Table 3. The STD clinic in Rotterdam.

std / year	1999	2000	2001
number of visitors tested for HIV	271	301	444
known to be HIV-positive	3	17	22
HIV-seroconverts (1)	12	7	13
HIV incidence	4.5	2.5	3.1
number of visitors tested for STD	318	351	476
early syphilis (2)	6 (1.9)	4 (1.1)	19 (4.0)
gonococcal infections (3)	26 (8.2)	23 (6.6)	52 (10.9)
rectal infection	10	14	19
urethral infection	17	9	40
tonsillar infection	2	2	3
chlamydial infections (3)	28 (8.8)	29 (8.3)	40 (8.4)
rectal infection	12	13	19
urethral infection	21	17	23
HBV immunity (anti-HBc-positivity)	31	27	44

(1) at the first visit: previously tested negative or were never tested for HIV
(2) primary, secondary and early latent syphilis (VDRL ≥ 1:8)
(3) number of infected visitors

Human papillomavirus infection and anal (pre)malignancies

Human papillomavirus (HPV) infection is the most common viral sexually transmitted infection in MSM and its prevalence is steadily increasing.[8] The prevalence of HPV was 28.2% in urethral swabs of more than 400, mostly heterosexual, men self-referring to an STD clinic in Tucson, Arizona. Most prevalent types were HPV-6, -53 and -84.[9]

In the Rotterdam cohort study, DNA of HPV types -6 to -33 in perianal swabs was detected in 36.3 % of the tested MSM. Types most often detected were HPV-6 and -16. In 49.1% of the perianal swabs from MSM DNA of the HPV types -35 to -74 was detected. Types most often detected in this group of HPV were HPV-52, -51 and -68 (chapter 6).

In MSM with a history of receptive anal intercourse the incidence of anal cancer related to the presence of HPV was estimated to be at least 44 times higher. The incidence of anal cancer among HIV-positive MSM may be about twice that of HIV-negative MSM.[10] Suppressed cellular immunity in HIV-positive individuals is associated with persistent HPV infection, which may trigger malignant transformation.[11] Large numbers of sexual partners, young age at the time of first (receptive anal) intercourse, a variety of concomitant rectal STDs and a history of rectal warts are all linked to the risk of anal cancer.[12]

MSM are definitely at a higher risk for HPV-related rectal cancers than other individuals. Recently, Piketty et al. reported that immune restoration under HAART in 45 HIV-positive MSM was not associated with a decrease in the prevalence of anal (H)SIL and HPV infection.[13] Goldie et al. stated that screening HIV-negative MSM for preneoplastic anal lesions with anal cytology every 2 or 3 years would benefit life expectancy and would be cost-effective. Annual screening was found to be cost-effective in HIV-positive MSM.[14,15]
At the Erasmus MC, University Medical Centre Rotterdam, 981 HIV-positive men and 453 HIV-positive women were monitored at the department of Internal Medicine from 1996 to 2003. Six (1.3%) females developed cervical cancer and 6 (0.6%) men developed anal cancer. Of these 6 men, 4 were MSM (personal communication, M.E. van der Ende MD PhD, Department of Internal Medicine, Erasmus MC). It is important to realize that this HIV cohort comprises a relatively large number of recently seroconverted individuals.
Anal HPV infections need continuing attention of all medical doctors involved in the care of HIV-positive MSM. To date, no high risk for penile cancer has been observed in MSM.
The ongoing vaccination trials are very promising and will probably lead to useful information for future immunization programs.[16] A trial in a cohort of young, sexually inexperienced MSM may be particularly interesting for studying the prevention of HPV-related disease.

Condylomata acuminata
Genital warts were a common STD in MSM participating in the Rotterdam cohort study. After gonorrhoea it was the most often mentioned STD. Almost 26% of the men stated to have or have had genital warts. In two-thirds of these cases the warts were located around the anus. The warts disappeared after a median period of 3 months (range 1 - 72 months). Having had anal warts did influence the sex life of 58% of the men. Of these men, 71% was 'anxious to infect sexual partners' and 70% stated to avoid certain sexual techniques while 52% considered themselves as 'dirty' (chapter 2).
Within another group of 100 MSM visiting the Rotterdam STD clinic who were invited to complete a questionnaire, 31% stated to have or have had genital warts. Most often these warts were located around the anus (67%), in the rectum (27%) or on the penile shaft (27%). The warts disappeared after a median period of 4.5 months (range 1 - 13 months). Having had anal warts did influence the sex life of 71% of the men. All of these men were 'anxious to infect sexual partners' while 63% considered themselves as 'dirty' . Of these individuals, 95% stated to avoid certain sexual techniques.

Table 4. Condylomata acuminata in the two groups of MSM.

characteristic	Rotterdam cohort study	visitors at the STD clinic in Rotterdam
number of MSM	243	100
median age (years, IQR) (1)	41 (34 - 49)	35 (27 - 42)
median number of lifetime partners (yr, IQR)	100 (30 - 300)	95 (20 - 200)
previous anal sex	85%	92%
previous condylomata acuminata	20%	14%
condylomata acuminata now (2)	6%	17%

(1) IQR denotes interquartile range
(2) at the time of completing the questionnaire

Table 5. Influence on sex life due to genital warts (mean scores).

	Rotterdam cohort study	visitors at the STD clinic in Rotterdam
avoids certain sexual techniques	2.9	3.2
anxious to infect sexual partner	2.8	3.7
considered himself as 'dirty'	2.1	2.7
sexual intercourse with fewer partners	2.0	2.2
less often sexual intercourse	2.0	2.6
never thinks about genital warts during sex	1.2	1.1

1 = does strongly disagree; 2 = does disagree; 3 = does agree; 4 = does strongly agree

HIV treatment-related optimism

From 1996 onwards, cases of rectal gonorrhoea and syphilis in MSM in Amsterdam increased steeply and reached levels comparable with those in the mid-1980s[17]. This indicates that the risk of transmission of HIV has substantially increased. The causal influence of availability of HAART is illustrated by increased risk-taking in HIV-positive men who experienced positive virological and immunological effects of treatment.[18] Proof for increased HIV infection is provided by a retrospectively documented increase in HIV infections in MSM visiting the Municipal STD clinic in Amsterdam.[19] These trends in MSM in Amsterdam corresponded to reports from cities in other countries.[20,21]

Unfortunately, prevention responses continue to lag behind, at least partially because increased risk-taking in MSM in the Netherlands is not extensively documented. Behavioural research should thus assess trends in risk-taking and the relation to infection rates. Further research

needs to establish psychosocial processes that underlie changed practices. Cross-sectional studies have shown that following the introduction of new anti-HIV treatments, perceptions of the severity of HIV infection and the probability of transmission of the virus have changed and resulted in an increased acceptability of unprotected intercourse. To date, however, a prospective design was used only in a few studies, which showed that optimistic beliefs were related to risk behaviours and the probability of STD- and HIV infections. These studies attest to a causal role of treatment-related optimistic beliefs, but leave several key issues unaddressed. Less is known of the small minorities of MSM who share optimistic treatment-related beliefs. In the Rotterdam cohort study less perceived HIV/AIDS threat since HAART availability was seen more often in MSM aged 40 years and older ($p = 0.025$). Less perceived need for safe sex since HAART availability was more common in bisexually orientated than homosexually orientated men ($p = 0.050$; chapter 7)
It is unknown whether the proportion of MSM that holds these beliefs increases over time. It is equally unknown what makes MSM likely to become optimistic.
A rational reasoning approach indicates that lower motivation to engage in safe sex would follow from more optimistic treatment-related beliefs. This lower motivation for safe sex, in turn, should precede risk-taking. A motivational reasoning approach posits that individuals may have a preference for unprotected intercourse, which can instigate a biased interpretation of available risk information. From this perspective, low motivation for safer sex would result in optimistic treatment-related beliefs that favour risk-taking. A third, dissonance reduction explanation holds that if an individual, for whatever reason, has engaged in risk-taking, this may instigate processes of cognitive adjustments to justify or excuse this behaviour.
The issue whether a lowered motivation for safe sex is a consequence of optimistic beliefs (rational reasoning) or predisposes individuals to hold optimistic beliefs (motivated reasoning) is particularly important. [20] In the former situation treatment-related beliefs would be a cause, which prevention efforts should aim to change, whereas in the latter they would be a justification, whereby prevention should focus on re-motivating MSM to practice safe sex.

The aim of further research should be to monitor sexual risk-taking in MSM and relate the behavioural trends to the rates of STD and HIV to establish changes in the prevalence of optimistic treatment-related beliefs, to assess whether these treatment related beliefs result from or produce lowered motivation to engage in safe sex, and study behavioural and psychosocial correlates of treatment-related beliefs. This research will provide information that may be used in programs aiming at the reduction of sexual risk behaviour in MSM.

Increased knowledge on STDs in the cohort period
In chapter 7 of this thesis we described the phenomenon of 'HIV-optimism'.
In multivariable analysis *less perceived HIV/AIDS threat since HAART availability* was associated with a higher cumulative incidence of STDs ($p = 0.005$). With regard to the new HIV infections, univariable analysis showed that treatment belief factors *perceiving less need for safe sex since HAART availability* was associated with HIV seroconversion ($p = 0.014$). Similar to that

observed in other studies, only a minority of MSM in our study (strongly) held optimistic beliefs concerning new HIV/AIDS treatments.[21,22]
The MSM had a mean score of 80% (range 21 - 100%) correctly answered items regarding HIV infection during all six cohort visits. The mean score of correctly answered items regarding STDs was 61% (range 7 - 96%). We concluded that MSM in this study seemed to be better informed on HIV infection compared with STDs ($p < 0.0005$).
When the scores of the participating men from the first three visits were compared with the last three visits, a significant increase in the score of correctly answered items regarding STDs was noted ($p < 0.0005$). No such an increase was observed in number of correctly answered items regarding HIV infection ($p = 0.66$), or regarding the mean scores of perceived severity of STDs and HIV infection or perceived susceptibility to STDs and HIV infection.
We conclude that participants in this study increased their knowledge on STDs during the cohort period. Repeating questions on STDs may increase the awareness or may stimulate those with insufficient knowledge to seek further information. The fact that this increase was not detected with regard to knowledge on HIV may be because of the fact that MSM were, from the start, much better informed on HIV infection than STDs.

Perceived STDs/HIV threat related to incidence of STDs and HIV infection
Finally, this thesis ends with the research concerning the possible associations between the cumulative incidence of STDs and HIV infection in MSM related to knowledge, perceived susceptibility and perceived severity of STDs and HIV infection.
In this study we concluded, that on the one hand, a high perceived severity of HIV infection marginally decreased the likelihood of infection with STDs ($p = 0.053$). On the other hand, the perceived threat of becoming infected with STDs did not have the same effect on HIV.
To our knowledge, studies on the relation between perceptions of threat and incidence of STDs and HIV infection have not been published previously, but provide an important avenue for research with the aim to contribute to an understanding of epidemiological trends. Due to the limitations of the study, the way perceived severity of HIV infection influences (sexual) behaviour that protects against STDs remains to be studied in more detail. Such an investigation may provide important information on psychosocial processes that co-determine disease outcomes and may contribute to the development of health promotion programs that support MSM in achieving a reduction in sexual risk behaviour.
It is of interest to find that a high perceived severity of HIV infection marginally decreased the likelihood of STDs. This indicated that MSM with higher perceived threat of HIV changed their (sexual) behaviour to reduce the likelihood of STDs. Additional analyses showed that MSM with higher perceived threat of HIV infection were significantly younger than MSM with lower perceived threat of HIV infection ($p = 0.013$). However, no differences were found regarding the number of sexual partners in the preceding 6 months or the practise of anal sexual intercourse ($p = 0.10$ and $p = 0.84$ respectively). The exact way in which perceived severity of HIV infection affects sexual behaviour remains unclear at present and more research is needed to establish how perceived severity of HIV infection influences both the (sexual) behaviour and the incidence of STDs.

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chapter 10

summary

A general introduction is presented in chapter 1. The Rotterdam cohort study (ROHOCO) took place from February 1999 to January 2002 at the sexually transmitted diseases (STDs) clinic of the department of Dermatology and Venereology of the Erasmus MC, University Medical Centre Rotterdam, The Netherlands.
The aim of our study was to monitor the cumulative incidence of STDs and HIV infection in men who have sex with men (MSM) and to longitudinally investigate the associated behavioural changes during the three-year cohort study. Apart from behavioural aspects, highly active antiretroviral therapy (HAART) and post-exposure prophylaxis (PEP) treatment beliefs as well as determinants of health, knowledge of transmission of HIV and STDs, perceived severity of different STDs and HIV infection and perceived susceptibility to certain STDs and HIV infection were compiled in order to examine associations with the cumulative incidence of STDs and HIV infection.

Information on demographics, behavioural data and self-reported earlier STDs is presented in chapter 2. From February 1999 to February 2000, a total of 286 MSM were recruited to participate in the Rotterdam cohort study.
More than 77% of these men were from the Rotterdam region and a majority (88%) were homosexually orientated. Up to 43% of the men had high education (college degree or equivalent). The median age of the participants was 39.5 years at enrolment and almost 60% lived alone.
Less than 40% had a religious denomination, mostly Protestant or Catholic. The vast majority (95%) were native Dutch.
Of all men, 60% had a steady partner. Almost 80% of all MSM with a steady partner also had sex with casual male partners during the previous six months.
The median number of lifetime sex partners was 100. Nearly 18% of the men stated to have had over 500 lifetime sex partners. MSM with a lower education had their first sexual intercourse with a male partner at an earlier age than those with a higher education (median age 17 years versus 19.5 years respectively). Generally, homosexually orientated men had their first anal sexual intercourse at an earlier age than bisexually orientated men (median age 22 versus 29 respectively). Of all participants, nearly 70% stated to have had anal sex regularly. Another 30% stated never to have had anal sex or used to having had it more than 6 months ago. Of those who had anal sex regularly, between 25 and 30% stated to 'always' use condoms.
At the first cohort visit, almost 40% of the MSM had never been tested for HIV. Almost 43% stated to have never had an STD in the past. The most frequent self-reported STDs were gonorrhoea (27%) and genital warts (26%). At the first cohort visit 26% of all MSM were hepatitis B immune. Only one-half of these men were aware of this immunity. All uninfected

participants were strongly advised to undergo vaccination for hepatitis A and B at the department of Infectious Disease Control of the local Municipal Health Service.

A study in which the possible changes in the prevalence of STDs and HIV in those visiting the STD clinic of the Erasmus MC in the period 1996 to 2000 were investigated is described in chapter 3. The age, the gender, the ethnic background, the sexual preference, the intravenous drug use and the prevalent STDs or HIV infections were analysed and compared in all who visited the clinic. The prevalence of HIV infection among the clinic visitors remained rather stable and was between 0.4% (2000) and 0.8% (1997). Most new HIV cases were encountered in the group of men who have sex with men (MSM). The prevalence of gonococcal infections and chlamydial infections significantly increased among heterosexual men and heterosexual women (p-values between < 0.0005 and 0.021). Among homo- and bisexual men a significant increase was noted only in chlamydial infections ($p = 0.021$).
A substantial decline in the number of cases of early syphilis was seen in all groups, with the exception of MSM.
The increased rate of gonorrhoea seen in heterosexual patients was in line with the data from Amsterdam. Whereas in Amsterdam an increase in rectal gonorrhoea and early syphilis was found in MSM, we did not observe such a rise. The difference in the rates of STDs in MSM in Amsterdam and Rotterdam may be explained by assuming on the one hand, that the MSM population in Amsterdam and Rotterdam have different sexual networks. On the other hand, it might well be possible that this increase in the rate of STDs in MSM in Amsterdam preceded such an increase of STDs in MSM in the Rotterdam area.
We started the Rotterdam cohort study in 1999 to be able to longitudinally investigate an early increase in the rate of STDs and HIV infections in Rotterdam.

Chapter 4 concerns a study which aimed at answering the question whether MSM visiting the STD clinic and those participating in the MSM cohort were different with regard to demographic characteristics, sexual behaviour and STD/HIV prevalence. Almost all available information on risky sexual behaviour and the prevalence of STDs and HIV among MSM was obtained from data of those visiting the STD clinic. Neither MSM visiting an STD clinic, nor participants of a cohort study consisted of unbiased groups of MSM. Recruitment of study participants was always prone to selection bias. Comparison of data from both groups of MSM allowed a more general assessment of behavioural indicators and possible risk factors for STDs and HIV.
Data from MSM presenting at the STD clinic (group I; $n = 318$) were compared with those participating in the cohort (group II; $n = 286$). All males underwent a routine venereological examination.
Men in group II were more often older ($p < 0.0005$), of Dutch descent ($p < 0.0005$) and had more sexual partners ($p < 0.0005$). New cases of HIV infection were detected more often in group I ($p = 0.04$). Urethral gonococcal infection was also significantly more prevalent in group I ($p = 0.003$).

Multivariable analyses showed that males presenting at the STD clinic (group I) were at a higher risk for urethral gonorrhoea ($p = 0.002$; OR = 6.99). This difference could not be explained by other factors. It was not unexpected that more individuals from group I presented with symptomatic STDs than from group II. Their reason to call in was mostly related to the experienced (urethral) symptoms.
However, the higher prevalence of HIV infection in group I was associated with a higher prevalence of recent STDs ($p = 0.016$; OR = 3.56), more often concomitant urethral gonorrhoea at the time of the visit ($p = 0.014$; OR = 6.82), over ten sexual partners in the previous six months ($p = 0.016$; OR = 2.89) and a larger number of men of non-Dutch descent ($p = 0.006$; OR = 4.22).
Men in group II seemed to be more sexually active and more sexually experienced, based on their age, higher number of episodes of STDs in the past and frequent changes of sexual partners. However, MSM voluntarily participating in the cohort study may be cautious and less at risk of an STD.

Chapter 5 is devoted the Rotterdam cohort study on human papillomavirus infection (HPV). HPV is the most common sexually transmitted viral infection and is related to the prevalence of penile and anal cancers and high-grade anal squamous intraepithelial lesions (HSIL). Some studies showed that MSM who stated to have had receptive anal sex had a 44 times higher incidence of anal cancer; HIV-positive MSM may even have a two times higher incidence than HIV-negative MSM. Persistent so-called 'high-risk' HPV-types (16, 18, 31 and 33) are especially related to (pre)malignant anal lesions. The use of highly active antiretroviral therapy (HAART) in HIV-positive MSM does not influence the risk of anal HSIL.
This cross-sectional HPV study was undertaken to establish the prevalence of both anal and coronal sulcus HPV infection, and to identify sexual behavioural risk factors related to the presence of HPV infection. In our study, HIV positivity was associated with a higher prevalence of anal high-risk HPV types ($p = 0.007$). Two or more different types of HPV were more often found in HIV-positive MSM ($p = 0.006$). Of all HIV-positive men, up to 65% had an anal HPV infection compared with 33% in HIV-negative individuals ($p = 0.015$). There was no association between HIV serostatus and the prevalence of coronal sulcus HPV infection ($p = 0.492$). Possible risk factors associated with the presence of anal HPV infection were a concomitant anal infection with *Chlamydia trachomatis*, gonococci, or herpes simplex virus ($p = 0.059$). No sexual behaviour determinants for the presence of HPV were found.

A sequel of the HPV study described in chapter 5 is presented in chapter 6. The main goal was to study the clearance and the acquisition of anal HPV infection and to investigate the possible differences between HIV-positive and HIV-negative cohort participants. Anal cancer is not common in Western Europe and the USA, with an incidence in the general population of approximately 7-9 per million. However, there is evidence that persistent high-risk HPV types that are causally linked to cervical cancer may also be linked to anal cancer, particularly in HIV-positive MSM practising receptive anal sexual intercourse.

Data of two planned cohort visits with a median interval of 21 months were compared. The incidence of anal HPV-16 and -31 infection showed a close to significant association with HIV-positivity (p = 0.059 and 0.068 respectively). The tendency to persist was significantly higher for HPV type 31 in the anal region of HIV-positive MSM compared with HIV-negative MSM (p = 0.036).
Anal cancer screening should be promoted particularly in HIV-positive individuals to prevent HPV-related malignancies. Life expectancy of HIV-positive individuals increases significantly because of HAART. As antiretroviral therapy does not seem to influence HPV persistence, HIV-positive MSM appear to have a higher risk for developing anal cancer. Understanding the epidemiology of anal HPV infection is important for the prevention of HPV-related disease and may provide data which may also be used for prevention and future immunization programs.

The phenomenon of 'HIV-optimism' is discussed in chapter 7. In some studies concerns on a potential increase in risky sexual behaviour because of the widespread availability and use of effective antiretroviral treatment (HAART), and the use of post-exposure prophylaxis (PEP) by MSM were expressed. The aim of this study was to prospectively investigate the association between HAART- and PEP-related beliefs and cumulative new STD- and HIV infections in HIV-negative MSM participating in the Rotterdam cohort study. We focused on STD/HIV diagnoses, rather than data on self-reported unprotected (receptive anal) sexual contacts. A recent study from Amsterdam showed an association between the change to unprotected receptive anal sex in MSM and reduced HIV/AIDS threat because of HAART availability.
In general, the participants in the Rotterdam cohort study were quite realistic on the effectiveness and the consequence of HAART and PEP. The majority (72.5%) of MSM (strongly) disagreed with belief statements measuring less perceived threat of HIV/AIDS and (strongly) disagreed with the idea that safe sex was less necessary because of the availability of HAART (96.6%) or PEP (91.3%). Only a minority (6.6%) of MSM in our study (strongly) held the belief that new HIV/AIDS treatments can eradicate the virus from a person's body.
In multivariable analysis *less perceived HIV/AIDS threat since HAART availability* was associated with a higher cumulative incidence of STDs (p = 0.0005). With regard to new HIV infections, univariable analysis showed that treatment belief factor *perceiving less need for safe sex since HAART availability* were associated with HIV seroconversion (p = 0.014). Nevertheless, our findings supported the assumption that a decreased perception of HIV/AIDS threat because of HAART availability led to an increased incidence of STD- and HIV infections.
The advice on the use of condoms during anal sex is important in the light of (long-term) side effects of HAART and PEP, the recent increase in the incidence of HIV infection worldwide, and the increasing transmission of drug-resistant HIV-1 strains. Advice on prevention should also include the fact that, although progress has been made on the treatments, there still is no cure for HIV and some patients are non-responsive to antiretroviral therapies. Finally, it is necessary to stress the fact that an undetectable viral load does not eliminate the risk of infection.

In the studies described in chapter 8, we longitudinally investigated whether issues such as perceived severity of, and perceived susceptibility to STDs and HIV infection, as well as the knowledge on STDs and HIV infection, were associated with the incidence of new STD- and HIV infections in MSM. These issues were obtained from the widely used 'health belief model' (HBM), a behavioural change model.
At the beginning, the three-year cohort study population consisted of 276 HIV-negative MSM. Data were obtained from each patient, at five or six planned visits with a 6-month interval. Data on the cumulative incidence of STDs and new HIV infections, and the perceived severity of and perceived susceptibility to STDs and HIV infection, as well as knowledge on STDs and HIV infection were compiled using self-administered questionnaires.
During the cohort study, 14 MSM HIV-seroconverted and 40 % of all men were diagnosed with at least one STD.
Knowledge on HIV infection in the MSM was rather high (83% correct answers). The participants seemed to be more informed on HIV infection compared with STDs (83 versus 63% correct answers respectively). HIV infection was perceived as being more severe than an STD.
In multivariable analyses, high numbers of sexual partners during the previous 6 months was associated with HIV seroconversion ($p = 0.006$; OR= 1.04), and anal intercourse in the preceding six months was associated with STDs ($p = 0.038$; OR = 2.06). High perceived severity of HIV infection almost significantly ($p = 0.053$; OR = 0.80) protected against STDs. The majority of MSM who HIV seroconverted (92%), also had an STD at one or more of the cohort visits. Increased knowledge on or high perceived susceptibility to STD and HIV infection was not associated with the actual risk of STDs or HIV infection.
A high perceived severity of HIV infection seems to induce sexual behaviour which protects against STDs. More research is needed to establish the process by which perceived severity of HIV influences sexual behaviour and incidence of STDs.

chapter 11

samenvatting

Hoofdstuk 1 is een algemene inleiding. Het Rotterdamse homocohort onderzoek (ROHOCO) vond plaats in de periode februari 1999 tot januari 2002 op de SOA-polikliniek van de afdeling Dermatologie en Venerologie van het Erasmus MC te Rotterdam.
De doelstelling van het onderzoek was de cumulatieve incidentie van SOA en HIV infecties en daarmee geassocieerde gedragskenmerken bij mannen die seks hebben met mannen (MSM) te onderzoeken. De duur van het onderzoek was drie jaar. Naast gedragskenmerken waren opvattingen over behandeling met antiretrovirale medicatie zoals 'highly active antiretroviral therapy' (HAART) en de zogenaamde postexpositie profylaxe (PEP), kennis over besmettingswijzen van SOA en HIV, de ingeschatte ernst van verschillende SOA en HIV en de ingeschatte bevattelijkheid voor diverse SOA en HIV onderwerp van studie.

In hoofdstuk 2 worden demografische gegevens, gedragsgegevens en zelf gerapporteerde gegevens over doorgemaakte SOA van de onderzochte populatie vermeld. Van februari 1999 tot februari 2000 werden 286 MSM geïncludeerd in het Rotterdamse cohort onderzoek.
Meer dan 77% van alle deelnemers kwam uit (de directe omgeving van) Rotterdam en de meerderheid (88%) was homoseksueel georiënteerd. Ongeveer 43% was hoog opgeleid (HBO of universitaire opleiding). De mediane leeftijd van de deelnemers was 39,5 jaar bij aanvang van het onderzoek en circa 60% van de deelnemers woonde alleen.
Iets minder dan 40% van de mannen had een geloofsovertuiging; meestal was dit protestant of katholiek. Het overgrote deel (95%) was autochtone Nederlander.
Ongeveer 60% van de deelnemers had een vaste partner. Van alle mannen met een vaste partner had ongeveer 80% in de afgelopen 6 maanden ook seks gehad met zogenaamde 'losse' partners.
Het mediane aantal seks partners tijdens het gehele leven was 100. Ongeveer 18% van de mannen gaf aan met meer dan meer dan 500 partners seks te hebben gehad. Lager opgeleide mannen hadden hun eerste seksuele contact met een man op een jongere leeftijd dan hoger opgeleide mannen (mediane leeftijd 17 respectievelijk 19,5 jaar). Uitsluitend homoseksueel georiënteerde mannen hadden in het algemeen hun eerste anale seksuele contact op een jongere leeftijd dan biseksueel georiënteerde mannen (mediane leeftijd 22 respectievelijk 29).
Van alle deelnemers gaf bijna 70% aan regelmatig anale seks te hebben gehad gedurende de voorafgaande zes maanden. De overige 30% had nooit anale seks, of langer dan een half jaar geleden. Van de mannen die regelmatig anale seks hadden, gaf 25 tot 30% aan altijd condooms te gebruiken.
Bij het eerste bezoek bleek ruim 40% van alle MSM nog nooit op HIV getest te zijn. Circa 43% vertelde nooit een SOA te hebben gehad. De meest gerapporteerde doorgemaakte SOA waren gonorroe (27%) en genitale wratten (26%).

Tijdens het eerste bezoek bleek 26% van de mannen hepatitis B immuun te zijn. Ongeveer de helft van deze mannen was hiervan op de hoogte. Alle niet-geïnfecteerde deelnemers kregen het advies zich te laten vaccineren tegen hepatitis A en B bij de 'GGD Rotterdam en omstreken'.
In hoofdstuk 3 worden de veranderingen in de prevalentie van SOA en HIV onderzocht op de Rotterdamse SOA-polikliniek in de periode 1996 tot 2000. Van alle bezoekers werden leeftijd, geslacht, etnische achtergrond, seksuele oriëntatie, eventueel intraveneus druggebruik en geconstateerde SOA en HIV infecties geanalyseerd en vergeleken.
De prevalentie van HIV infecties onder de bezoekers was redelijk stabiel in deze periode en varieerde tussen 0,4% (in 2000) en 0,8% (in 1997). De meeste nieuwe HIV infecties werden geconstateerd bij MSM. De prevalentie van gonorroe en chlamydia infecties nam significant toe onder heteroseksuele mannen en vrouwen (p-waarden tussen < 0,0005 en 0,021). Bij MSM was in deze periode alleen sprake van een significante toename van chlamydia infecties (p = 0,021).
Een forse daling van het aantal vroege gevallen van syfilis werd gezien in alle groepen, met uitzondering van de MSM. De genoemde toename van gonorroïsche infecties werd ook gezien op de Amsterdamse SOA-polikiniek. In Amsterdam was er onder MSM echter ook sprake van een toename van rectale gonorroe en vroege vormen van syfilis, een waarneming die niet op de Rotterdamse SOA-polkliniek werd gedaan. Het verschil in SOA prevalentie tussen Amsterdam en Rotterdam kan waarschijnlijk voor een belangrijk deel verklaard worden met de aanname dat MSM in Amsterdam en Rotterdam hun eigen, gescheiden seksuele netwerken hebben. Ook zou de toename van rectale infecties met gonorroe en vroege gevallen van syfilis onder MSM in Amsterdam een voorbode kunnen zijn voor een toename van deze SOA in Rotterdam. Om mogelijke trends longitudinaal te kunnen vervolgen, startte in 1999 het Rotterdamse cohort onderzoek.

In hoofdstuk 4 werd onderzocht of MSM die de SOA-polikliniek in 1999 bezochten, verschilden van de MSM uit het Rotterdamse cohort onderzoek met betrekking tot demografische gegevens, seksueel gedrag en prevalentie van SOA en HIV. Bijna alle gegevens over (risicovol) seksueel gedrag en prevalentie van SOA en HIV zijn afkomstig van SOA-poliklinieken. MSM die de SOA-polikliniek bezoeken en MSM die vrijwillig deelnemen aan een cohort onderzoek zijn geselecteerde groepen. Vrijwillige deelname aan een onderzoek geeft kans op selectiebias. Vergelijking van deze beide groepen geeft dan ook een completer beeld over gedragsindicatoren en mogelijke risicofactoren voor SOA en HIV in de totale groep van MSM in Rotterdam.
De gegevens van 318 MSM die op eigen initiatief de SOA-polikliniek bezochten (groep I), werden vergeleken met 286 cohort onderzoek deelnemers (groep II). Alle mannen ondergingen een venerologisch onderzoek.
De MSM in groep II waren gemiddeld ouder (p < 0,0005), vaker van autochtone Nederlandse afkomst (p < 0,0005) en hadden meer seks partners gehad in de laatste zes maanden (p < 0,0005). Nieuwe HIV infecties werden vaker gezien in groep I (p = 0,04), Ook urethrale gonorroe kwam significant vaker voor in groep I (p = 0,003).

Multivariabele analyse toonde aan dat mannen die uit eigen beweging de SOA-polikliniek bezochten een groter risico hadden op een urethrale gonorroe (p = 0,002; OR = 6,99). Het is geen verrassing om te constateren dat er meer symptomatische SOA voorkwamen in groep I. De reden, van mannen uit deze groep, om naar de SOA-polikliniek te komen was namelijk meestal de aanwezigheid van (urethrale) klachten.
De hogere prevalentie van HIV infecties in groep I bleek geassocieerd met een hogere prevalentie van kortgeleden gediagnosticeerde SOA (p = 0,016; OR = 3,56), meer gelijktijdig aanwezige urethrale gonorroe (p = 0,014; OR = 6,82), meer dan tien sekspartners in de laatste 6 maanden (p = 0,016; OR = 2,89) en een niet-autochtone Nederlandse achtergrond (p = 0,006; OR = 4,22).
De MSM in groep II leken seksueel actiever en seksueel meer ervaren gebaseerd op hun leeftijd, hun frequentere SOAs in het verleden en het grotere aantal seks partners gedurende het gehele leven. Vrijwillig aan het cohort onderzoek deelnemende MSM lijken voorzichtiger individuen te zijn en hebben dankzij genomen voorzorgsmaatregelen wellicht een kleinere kans op het krijgen van een SOA of HIV infectie.

Hoofdstuk 5 is een studie naar de prevalentie van humaan papillomavirus (HPV) infectie. HPV is de meest voorkomende virale SOA en is geassocieerd met maligniteiten aan penis en anus en premaligne huidafwijkingen zoals 'high-grade squamous intraepithelial lesions' (HSIL). Uit onderzoek blijkt dat MSM die receptieve anale seks hebben, een 44-maal grotere kans hebben op anale maligniteiten. HIV-positieve MSM die receptieve anale seks hebben, lijken zelfs een 88-maal grotere kans te hebben. Vooral de persisterende infecties met zogenaamde 'hoog-risico' HPV-types (16, 18, 31 en 33) zijn gerelateerd met (pre)maligne (anale) afwijkingen. Het gebruik van 'highly active antiretroviral therapy' (HAART) bij HIV-positieven heeft geen invloed op het risico op anale maligniteiten.
Deze cross-sectionele HPV studie werd verricht om de prevalentie van zowel HPV infecties van de anus als de sulcus coronarius te bepalen en om demografische factoren en seksuele gedragsfactoren te ontdekken die invloed hebben op deze prevalentie.
In onze studie bleek HIV-seropositiviteit geassocieerd met een hogere prevalentie van anale 'hoog-risico' HPV types (p = 0,007). Het gelijktijdig aanwezig zijn van twee of meer HPV types werd vaker gezien bij HIV-positieve MSM (p = 0,006). Van alle HIV-positieve mannen bleek ongeveer 65% anaal een HPV infectie te hebben, vergeleken met 33% bij de HIV-negatieve mannen (p = 0,015). Er bleek geen associatie aanwezig te zijn tussen HIV serostatus en de prevalentie van HPV infecties ter plaatse van de sulcus coronarius (p = 0,492).
Een mogelijke risicofactor die geassocieerd bleek met de aanwezigheid van anale HPV infecties was de gelijktijdige aanwezigheid van infecties met *Chlamydia trachomatis*, gonorroe en herpes simplex (p = 0,059). Er kon geen relatie worden aangetoond tussen seksuele gedragsfactoren en de aanwezigheid van HPV.

Het onderzoek in hoofdstuk 6 is een vervolg op de HPV studie in hoofdstuk 5. Het doel hiervan was spontane klaring en acquisitie van anale HPV infecties te onderzoeken en mogelijke verschillen te ontdekken tussen HIV-positieve en HIV-negatieve MSM. Anuskanker

is tamelijk zeldzaam in West-Europa en de Verenigde Staten en heeft een incidentie van ongeveer 7 tot 9 per miljoen mensen. Uit onderzoek blijkt dat de persisterende 'hoog-risico' HPV types die een rol spelen bij het ontstaan van het cervixcarcinoom, waarschijnlijk ook betrokken zijn bij anuskanker.
Gegevens van twee cohort bezoeken met een mediane tussenperiode van 21 maanden werden met elkaar vergeleken. De incidentie van anale HPV infecties met type 16 en 31 toonde een bijna significante associatie met HIV-positiviteit (p = 0,059 en 0,068 respectievelijk). Bij HIV-positieve MSM bleek HPV type 31 significant langer rond de anus te persisteren vergeleken met HIV-negatieve MSM (p = 0,036).
Screening op anuskanker moet gepromoot worden, zeker onder HIV-positieve MSM, om HPV-gerelateerde maligniteiten te voorkomen. Omdat de levensverwachting bij HIV-positieve individuen is gestegen dankzij het gebruik van HAART, terwijl deze behandeling geen invloed heeft op de persistentie van HPV infecties, hebben HIV-positieve MSM een groter risico op het ontwikkelen van anuskanker.
Kennis over de epidemiologie van anale HPV infecties is van belang met het oog op de preventie van HPV-gerelateerde afwijkingen. Deze gegevens kunnen tevens gebruikt worden voor toekomstige vaccinatie programma's.

Hoofdstuk 7 gaat over het fenomeen 'HIV optimisme'. Uit nationale en internationale onderzoeken blijkt dat de toename van risicovolle seksuele contacten bij MSM waarschijnlijk deels toe te schrijven is aan de succesvolle introductie van HAART en het ter beschikking komen van de zogenaamde post-expositie profylaxe (PEP). Het doel van deze studie was het prospectief onderzoeken van associaties tussen HAART- en PEP-gerelateerde overtuigingen en de cumulatieve incidentie van SOA en HIV infecties bij HIV-negatieve MSM. In een recent onderzoek in Amsterdam werd een associatie gevonden tussen verandering van beschermde naar onbeschermde receptief anale sekscontacten en een als minder ernstig ervaren HIV/AIDS dreiging dankzij het ter beschikking komen van HAART. In onze studie werd gekeken naar SOA en HIV diagnoses als uitkomstmaat en niet naar zelf-gerapporteerd gedrag over onbeschermde sekscontacten.
Over het algemeen bleken de deelnemers van het Rotterdamse cohort onderzoek een realistische kijk te hebben op de effectiviteit en de consequenties van HAART en PEP. Het overgrote deel (73%) bleek het (sterk) oneens te zijn met de stellingen die een minder ernstig ervaren bedreiging door HIV/AIDS suggereerden en waren het (sterk) oneens met het idee dat veilig vrijen minder noodzakelijk was sinds het beschikbaar komen van HAART (97%) of PEP (91%). Een klein percentage (7%) was ervan overtuigd dat de nieuwe behandelingsmogelijkheden voor AIDS het HIV volledig uit iemands lichaam konden 'uitroeien'.
Uit univariabele analyse bleek dat een minder ervaren noodzaak voor veilige seks sinds het beschikbaar komen van HAART, geassocieerd was met HIV seroconversie (p = 0,014). Een als minder ernstig ervaren bedreiging door HIV/AIDS, sinds het beschikbaar komen van HAART, was in multivariabele analyse geassocieerd met een hogere cumulatieve incidentie van SOA (p = 0,0005).

Onze bevindingen ondersteunen de aanname dat een minder ernstig ervaren bedreiging door HIV/AIDS ten gevolge van ter beschikking gekomen HAART kan leiden tot een toename van de incidentie van SOA en HIV.
Het gebruik van condooms tijdens anale seks, ter preventie van SOA en HIV, is van groot belang gezien de wereldwijde toename van HIV infecties, de toename van de overdracht van voor bepaalde medicamenten ongevoelige HIV-1 stammen en de (lange termijn) bijwerkingen van HAART en PEP. Gezien de toename van risicovolle sekscontacten bij MSM, moet er getracht worden over te brengen dat er nog geen genezingsmogelijkheden zijn voor HIV infecties en dat sommige patiënten niet of slechts onvoldoende reageren op de behandeling. Het blijft belangrijk om uit te leggen dat een niet-detecteerbare 'viral load' niet inhoudt dat het HIV volledig uit het menselijk lichaam is verdwenen.

Tenslotte wordt in hoofdstuk 8 in een longitudinale studie onderzocht of onderwerpen als ervaren ernst van SOA en HIV, ervaren bevattelijkheid voor SOA en HIV en kennis over SOA en HIV bij MSM geassocieerd zijn met een hogere cumulatieve incidentie van SOA en HIV. Deze onderwerpen zijn onderdeel van het veel gebruikte 'health belief model' (HBM), een model waarmee gedragsverandering verklaard kan worden.
Van alle 276 HIV-negatieve MSM werden tijdens minimaal vijf van de zes halfjaarlijkse cohort bezoeken gegevens verzameld. Naast gegevens over de cumulatieve incidentie van SOA en HIV werd met behulp van vragenlijsten informatie verzameld over ervaren ernst van SOA en HIV, ervaren bevattelijkheid voor SOA en HIV en kennis over SOA en HIV bij de deelnemers.
Tijdens de driejarige cohort studie seroconverteerden 14 MSM voor HIV en werd bij 40% van de deelnemers een of meerdere SOA's geconstateerd.
De kennis over HIV infectie was hoog bij de MSM (83% van de vragen correct beantwoord). De deelnemers waren meer op de hoogte van HIV dan van SOA (respectievelijk 83 en 63% van de vragen correct beantwoord). HIV infecties werden ook als ernstiger ervaren dan SOA. Uit multivariabele analyses bleek dat anale seks gedurende de voorafgaande zes maanden was geassocieerd met een hogere cumulatieve incidentie van SOA ($p = 0{,}038$; OR = 2,06). Een hoge ervaren ernst van een HIV infectie gaf een bijna significante bescherming tegen SOA ($p = 0{,}053$; OR = 0,80) Het overgrote deel van de MSM die HIV-seroconverteerden (92%) bleek een of meerdere SOA te hebben gehad gedurende het onderzoek. Veel kennis over SOA en HIV of een hoge ervaren bevattelijkheid voor SOA of HIV bleek niet geassocieerd met een kleinere kans op een SOA of HIV infectie.
Een hoge ervaren ernst van een HIV infectie beschermt via niet nader bekend (seksueel) gedrag tegen SOA. Meer onderzoek naar de manier waarop een hoge ervaren ernst van een HIV infectie seksueel gedrag beïnvloedt en een lagere incidentie van SOA veroorzaakt, is nodig.

dankwoord

Dat niet altijd uitsluitend wetenschappelijke belangstelling ten grondslag ligt aan medisch onderzoek blijkt wel uit de ontstaansgeschiedenis van dit promotieonderzoek. De vrees meer onderzoek te moeten doen naar het ontstaan van de aandoening 'bacteriële vaginose', een van de meest voorkomende oorzaken van onwelriekende vaginale afscheiding, was wel de eerste aanzet tot het opstarten van de Rotterdamse homocohort studie (ROHOCO). Vooral het idee de vele duizenden verzamelde vaginale uitstrijkjes microscopisch te moeten onderzoeken op 'clues cells', een van de kenmerken van deze bacteriële aandoening, gaf me slapeloze nachten.
Dat we voor het ROHOCO de kunst grotendeels hebben afgekeken en leentjebuur hebben gespeeld bij de Amsterdamse homocohort studie is publiek geheim. Vooral mijn copromotor John de Wit, van oudsher betrokken bij de Amsterdamse studie, wil ik bedanken voor zijn adviezen voor de opzet, de uitvoering en zijn onmisbare bijdrage bij de beschrijving van de bevindingen in de artikelen in dit proefschrift. Ik kan me nog herinneren dat ik met het lood in de schoenen je de eerste keer opbelde met de vraag of we in Rotterdam niet wat vragenlijsten uit Amsterdam mochten lenen. Je vele ideeën voor de Rotterdamse studie verhoogden mijn ontzag voor je wetenschappelijke kennis en inzichten. Ik ben je ook dankbaar voor je bereidheid, ondanks al je vele andere activiteiten, naar mijn schrijfsels te kijken en commentaar terug te mailen. Dank je wel.
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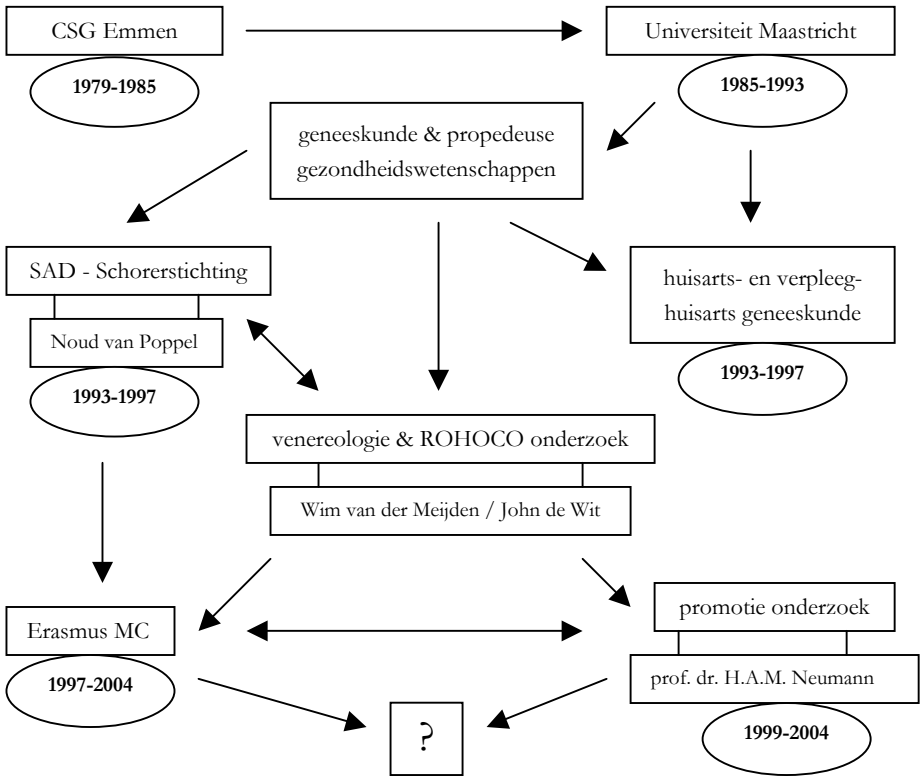
curriculum vitae

Op 8 januari 1967 wordt Eric Martin van der Snoek geboren in het Zuid Hollandse Reeuwijk. Het grootste deel van zijn jeugd brengt hij door in het Drentse Emmen waar hij de basisschool en voorbereidend wetenschappelijk onderwijs volgt. Op zijn achttiende vertrekt hij naar de Universiteit Maastricht om na zijn propedeuse gezondheidswetenschappen, geneeskunde te gaan studeren. Na het behalen van zijn bul in 1993 verhuist hij naar Schiedam en later naar Amsterdam om enkele jaren te werken in de huisarts- en verpleeghuisgeneeskunde.
Tijdens vrijwilligerswerk bij de Weekendpoli van de Stichting Aanvullende Dienstverlening (SAD) en later de Schorerstichting (supervisor Noud van Poppel) in de periode 1993 tot 1997 krijgt hij belangstelling voor de venereologie.
In 1997 solliciteert hij op de polikliniek Venereologie in Rotterdam waar hij twee jaar werkt als AGNIO voordat in mei 1999 zijn opleiding tot dermato-venereoloog start met als opleider prof. dr. Th. van Joost en vanaf 2002 prof. dr. H.A.M. Neumann. Enkele maanden daarvoor begint hij met de opzet van de Rotterdamse homocohort studie (ROHOCO) met begeleiding van dermato-venereoloog Wim van der Meijden van het Erasmus MC en gedragspsycholoog John de Wit van de Universiteit Utrecht.
Zijn werkzaamheden bij het ROHOCO eindigen zodra hij in mei 2004 zijn opleiding tot dermato-venereoloog voltooit.



list of abbreviations

AIDS	acquired immunodeficiency syndrome
CI	confidence interval
CT	*Chlamydia trachomatis*
DNA	desoxyribo nucleic acid
ES	early syphilis
FTA-abs	fluorescent treponemal antibody-absorption
GC	gonococcal infection
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSV	herpes simplex virus
IQR	inter-quartile range
IV	intravenous
MC	medical center
MSM	men who have sex with men
N	number
NE	not estimable
NG	*Neisseria gonorrhoeae*
NSU	non-specific urethritis
OR	odds ratio
PCR	polymerase chain reaction
PEP	postexposure prophylaxis
SD	standard deviation
STD	sexually transmitted disease
TPPA	treponema pallidum particle agglutination
VDRL	venereal disease research laboratory