Epidemiological studies of HIV infection in woman
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Chapter 1

Introduction
Introduction

Nowadays 15.7 million women world-wide live with human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS), 12.9 million in sub-Saharan Africa and 130 thousand in Western Europe; nearly 7.7 million women have already lost their lives to the disease [1]. Heterosexual transmission is now the major mode of HIV transmission, but because the first AIDS cases were diagnosed among homosexual men [2], the first and majority of epidemiological studies on the natural history of HIV infection have been conducted in that population. This accounts, at least in part, for the lack of data describing HIV infection in women, to whom the epidemic spread more recently. Since there is evidence that gender differences exist in the two markers of disease progression used as criteria for starting antiretroviral therapy (i.e., CD4 lymphocyte count and HIV RNA levels), extrapolation of results from studies in men might be inadequate for the initiation and monitoring of therapy in women. The access to health care, prescription of treatment, and compliance with treatment are important for progression of HIV infection and these factors too could differ between women and men. Furthermore, specific aspects related to HIV infection in women including the impact of pregnancy and the occurrence of gynaecological disorders can be studied only in women. Thus, key issues in women such as incubation period, prognostic value of biological markers and cofactors of disease progression are still under debate and need to be clarified.

This chapter provides an introduction into the research presented in this thesis. In section 1.1, the natural history of HIV infection in men and women, and gender differences in the course of HIV infection is discussed. Specific aspects related to HIV infection in women, such as pregnancy, mother-to-child transmission, gynaecological disorders and co-infection with other sexually transmitted agents are presented in section 1.2. Section 1.3 gives a detailed description of the European Study on the Natural History of HIV Infection in Women, on which most of the present research is based. Section 1.4 and 1.5 give a brief description of two multicenter cohort studies among homosexual men - the Tricontinental Seroconverter Study and the combined hepatitis B vaccine trial cohorts in Amsterdam, New York City, and San Francisco – whose results are presented in chapter 2 and 3. The scope of this thesis is further outlined in section 1.6.

1.1 The natural history of HIV infection

After the first AIDS cases manifested in homosexual men in the early 1980s and an antibody test for HIV had become available, epidemiological studies on the natural history of HIV infection started among homosexual men [3-9], haemophiliacs [10-12] and injecting drug users (IDUs) [13-15]. Only recently cohort studies were started among heterosexually infected women [16-18]. In all these cohorts, the primary goal was to study the natural history of HIV infection, its pathogenesis, and the immunological and virological aspects of the infection. The natural history of HIV infection is studied by estimating the HIV incubation time from seroconversion to AIDS and death and by investigating the risk factors and markers for disease progression. Especially cohort studies of persons with a known interval of HIV
seroconversion (i.e., seroconverters) are valuable for understanding the natural history of HIV infection, because bias related to an unknown duration of infection is avoided [19,20]. The interval of seroconversion is often defined as the interval between the last negative and the first positive HIV test, but it can be based on other data, such as the presence of a symptomatic primary infection or reported risk behaviour. A disadvantage of most studies among seroconverters is the relatively small study size, because for most HIV-positive persons information on the interval of HIV seroconversion is not available. Furthermore, the number of seroconverters with known disease outcomes is limited by the relatively low incidence of HIV infection and the long follow-up time required for progression to AIDS and death. To overcome the problem of a small study size, data of several seroconverter studies can be pooled in multicenter studies. In this thesis, data of three different multicenter studies are presented and a description of the studies is given later in this chapter. Estimates of the median incubation period of AIDS, based on seroconverter studies, range from 8 to 16 years [21-25]. Variation in these estimates can be explained largely by differences in the age of the study population, but may also reflect differences in AIDS case definition, study design, and censoring strategies [26]. The median survival time following diagnosis of AIDS varies between 12 and 18 months [27]. When highly active antiretroviral therapy (HAART) became widely available in 1996 in most Western countries, the incubation time to AIDS increased, as did post-AIDS survival time [28-30]. With these improvements, as a consequence, the morbidity and mortality due to AIDS decreased [31,32].

For many years, the absolute number of CD4 lymphocytes was the primary marker to assess the stage of disease progression. Recently, when HIV-RNA levels (HIV viral load) could be determined, they provided another essential laboratory marker to predict and monitor disease progression [33]. Without intervention of antiretroviral therapy, the number of CD4 lymphocytes decreases whereas HIV-RNA levels increase in most subjects during the course of infection, but the variation between and within individuals is large. Both markers are routinely used as criteria for therapy initiation. In addition, other laboratory measures such as viral phenotype and T-cell function have been shown to be prognostic markers of disease progression [34,35].

During the two decades of AIDS research, many potential risk factors for disease progression have been studied. Of these, age alone has been consistently found as a risk factor, in such way that older persons progress to AIDS faster than younger ones [36]. Recently, genetic factors of the host that may influence the course of HIV infection have been described. For example, a deletion in the gene coding for the C-C chemokine receptor 5 (CCR5) and mutation in the gene coding for the C-C chemokine receptor 2 (CCR2) are associated with slower HIV disease progression [37-39]. Other risk factors which have been frequently studied include geographic region [40], mode of HIV transmission [41-46] and gender [47,48]. The last will be discussed in detail in the next section.
1.1.1 Gender differences
As a consequence of the major role of cohort studies among homosexual men, still too little attention is paid to biomedical aspects of HIV and AIDS in women. Variations in the natural history of HIV infection between men and women have implications for the management of HIV infection in women. So far, studies mainly conducted among male and female IDUs have demonstrated that the incubation time to AIDS and the survival following AIDS diagnosis do not differ by gender after adjustment for confounders such as age and access to antiretroviral therapy [42,46,49-52]. However, when several studies investigated sex differences in the incidence of AIDS-defining illnesses, differences were seen [53,54]. The development of an AIDS-defining illness, especially an opportunistic infection, is related to the degree of immunosuppression and to exposure to a pathogen. Because behaviour and social circumstances influence exposure to pathogens of HIV-related illnesses, one would expect variation in AIDS-defining illnesses by risk group and gender. Findings indicate that HIV-infected women appear to have higher rates of recurrent bacterial pneumonia and herpes simplex virus (HSV) ulcerations and lower rates of Kaposi’s sarcoma as AIDS-defining illnesses in comparison with men. The higher rate of bacterial pneumonia could be explained by the high percentage of women with a history of injecting drug use in these studies [53]. The higher rate of herpes simplex ulcerations is more difficult to explain but might be a result of a higher vulnerability of women than men to HSV [54]. The lower rate of Kaposi’s sarcoma is caused by a lower infection rate of human herpes virus 8 (HHV8) in women compared to homosexual men.

Various gynaecological disorders like cervical dysplasia, recurrent vaginal candidiasis, and pelvic inflammatory disease are unique manifestations of HIV infection in women [55,56]. Differences between men and women concerning other non-AIDS-defining clinical manifestations were studied in cohorts of IDUs [57,58]. The incidence of such manifestations including skin abscesses, endocarditis, orolabial herpes, oral candidiasis, genital herpes, and other sexually transmitted infections (STI) was higher among women than men in Amsterdam [58], although no differences were observed among IDUs in Baltimore [57].

There is evidence that throughout infection, CD4 lymphocyte counts are about 100 cells/μl higher in HIV-infected women than in HIV-infected men [59,60]. When several studies evaluated gender differences in HIV-RNA levels [61,62], levels early in HIV-infection were found to be approximately 50% lower in women than in men, but with ongoing HIV infection, this gender difference seems to disappear [62,63]. Because the absolute CD4 lymphocyte count and HIV-RNA levels are markers closely correlated with the stage of HIV infection, one could hypothesise that women may experience slower disease progression. However, as is mentioned before, most studies found no significant effect of gender on disease progression. Thus, the higher CD4 lymphocyte counts and lower HIV-RNA levels in women compared to men seem to have no functional significance. The possibility that women will be undertreated must nevertheless be carefully considered and needs further investigation, because the current treatment guidelines are based on results of studies among men.
Differences in CD4 lymphocyte counts between men and women exist in the general (HIV-uninfected) population [64,65], but not before the age of 15 years (i.e., before the menarche) or after the age of 50 (i.e., after the menopause). Furthermore, CD4 lymphocyte counts as well as HIV-RNA levels fluctuate in individual HIV-infected women during the menstrual cycle [66,67]. All these findings suggest that both of these markers are affected by changes in levels of women's reproductive hormones.

1.2 Aspects of HIV infection in women

1.2.1 Pregnancy

Since most HIV-infected women are of reproductive age, knowledge of the relationship between HIV-infection and pregnancy is an important public health issue and helps HIV-infected women to make a conscious decision concerning a pregnancy. Two aspects of this relationship will be considered. First of all, studies among pregnant (HIV-uninfected) women showed that the immune system changes during pregnancy, probably to prevent rejection of the foetus, which is foreign tissue from an immunological point of view. The absolute number of CD8 cells slightly drops during pregnancy, whereas the CD4 and CD8 percentages as well as the total immunoglobulin (Ig) A and M levels remain stable throughout pregnancy [68]. The absolute number of CD4 lymphocytes drops in the first trimester, probably as a consequence of higher concentrations of reproductive hormones in blood (i.e., progesterone and estradiol) but increases again in the second and third trimester, reaching pre-pregnancy level after delivery. Combining this information with the fact that CD4 decline is an important marker of HIV disease progression, it was suggested that pregnancy could accelerate disease progression, but no negative impact of pregnancy on disease progression of HIV-infected women has been demonstrated [68-72]. Secondly, there is growing evidence that the fertility of HIV-positive women is lower than that of HIV-negative women due to direct biological effects of HIV, such as increased menstrual disorders and a decreased production of spermatozoa [73]. Furthermore, co-infection with other sexually transmitted diseases, which is regularly observed in HIV-infected persons who do not have access to STI treatment, results in reduced fertility and foetal losses [73]. Several studies have found lower birth and pregnancy rates in HIV-positive women than in HIV-negative women [74-76]. However, it was not possible to determine whether these lower rates reflected reduced fertility due to HIV infection, a previous STI, or awareness of the HIV serostatus that might change reproductive decision-making. The decision to continue or abort a pregnancy is complex and strongly related to individual, social, and cultural values. In two studies among pregnant HIV-infected women, approximately 50% of all pregnancies ended in an induced abortion [77,78]. Recently, reproductive decision-making has perhaps been influenced by the effective measures now available to reduce vertical transmission and the positive effect of HAART on the life expectancy of HIV-infected women themselves. Therefore, one can anticipate that the incidence of pregnancies and the number of full-term pregnancies in HIV-infected women will increase in the coming years.
1.2.2 Mother-to-child transmission

Although pregnancy seems to have no effect on the health status of HIV-infected women themselves, these women are at risk of transmitting the virus to their foetus. Ninety percent of all HIV-infected children are infected through vertical transmission, which can occur during advanced pregnancy, delivery, or breastfeeding [79,80]. The risk of vertical HIV transmission during pregnancy and/or delivery ranges from 15-40%, depending on factors like the immune status, genital infections, HIV load, and nutritional status of the mother [81-85]. Prescription of zidovudine (AZT) to pregnant women and their new-borns decreases the risk of vertical transmission to as little as 8% [86]. Other effective measures, such as Caesarean section [87,88] and avoidance of breastfeeding, can further decrease this risk to 1-2% [89]. In developed countries, nowadays, Caesarean section is recommended and most women who are receiving HAART before pregnancy continue their treatment during pregnancy. Current guidelines indicate prescription of AZT to pregnant women who are not receiving treatment at the time they become pregnant or the nevirapine to the mother during labor [90]. Both drugs are prescribed to the child after delivery. Studies are in progress to investigate the toxic effects of exposure to antiretrovirals in infants. So far, results demonstrate that short-term effects are likely to be rare and outweigh by the proven benefit of reducing HIV transmission [91,92]. However, little is known about the long-term effects of these drugs. Prevention of mother-to-child transmission is one of the most important issues of HIV care in Africa, but the issue of breastfeeding and empowerment of women regarding sex-related issues need also more attention. However, prescription of preventive treatment is often unaffordable, and the use of bottle-feeding instead of breastfeeding increases the risk of serious infections due to polluted drinking water. Thus, despite all the progress made in prevention of mother-to-child transmission, most women in developing countries are not able to benefit from it. This painfully demonstrates the gap between developed and developing countries.

1.2.3 Gynaecological disorders and co-infection with other sexually transmitted agents

Amongst women, the most likely mode of HIV transmission is heterosexual intercourse. Besides HIV infection, women are also at risk to acquire other STIs. The interrelationship between HIV and other STIs is now well established; co-infection with other agents enhances the risk of HIV transmission, whereas HIV infection can alter the course of these other infections. Both ulcerative (e.g., genital herpes, chancroid, syphilis) and non-ulcerative (e.g., chlamydia, gonorrhoea, trichomoniasis) STIs promote HIV transmission, by augmenting HIV infectiousness and host susceptibility through biological mechanisms that may vary among specific STIs [93]. The risk to infect someone else with HIV is probably promoted by STI-related inflammatory reactions and disruption of mucosal barriers that facilitate HIV shedding in the genital tract [94]. Host susceptibility to HIV infection appears to increase due to STI-related development of inflammatory reactions with local accumulation of large numbers of macrophages and T-lymphocytes, the target cells for HIV, and disruption of mucosal barriers to infection. The risk of HIV-1 seroconversion is approximately two- to fivefold higher in persons diagnosed with
another STI than in persons without an STI after adjustment for sexual behaviour [93]. Prevention, early diagnosis and treatment of STIs in HIV-negative women at risk for HIV should therefore lead to a reduction of HIV transmission. Therefore, regular STI detection and treatment next to primary prevention should be implemented in HIV prevention programmes. The impact of other STIs on HIV disease progression has received little research attention, but results of the few available studies among homosexual men do not suggest a significant impact [95,96]. Whether other STIs influence HIV disease progression in women could be a subject for further investigation.

HIV infection alters the course of infection of other STI, resulting in a higher recurrence of chronic STI, especially in immunosuppressed women. These chronic infections include genital warts and cervical lesions that are caused by human papilloma viruses [97,98], and genital herpes that is caused by herpes simplex virus (mainly type 2). These two viruses commonly present in HIV-infected women will be discussed in detail below.

1.2.3.1 Human papilloma virus (HPV) infection

There are more than 100 different HPV types known at present. Thirty of them infect the genital mucosa and these are generally divided into low-risk and high-risk types based on their association with genital warts, cervical dysplasia and invasive cervical cancer (ICC). Of the high-risk types, HPV type 16 is the most common worldwide, followed by HPV types 18, 31 and 45 [99]. The association between HPV infection and ICC is well-established [100-103]. Data from epidemiological studies suggest that most women acquire HPV infection relatively early after initiation of sexual activity. The prevalence of HPV infection is estimated to be 1-6% in the general population. It is highest among women in their early twenties, but declines thereafter, suggesting that immune response to HPV may be either clear the infection or reduce it to undetectable levels [104]. Most HPV infections clear within one year [105].

Squamous intraepithelial lesions (SIL), a preliminary stage of ICC, are more likely to occur, progress and recur in HIV-infected women than in women without HIV, and the prevalence and severity of SIL appear to increase with increasing HIV-induced immunosuppression [106-112]. In an American study, 20% of all HIV-infected women developed SIL during three years of follow-up, in contrast to 5% of HIV-uninfected women. This highlights the importance of cervical screening programmes for HIV-infected women [113]. Persistent infection of the high-risk types of HPV is an important factor in the development of SIL [105,114]. HIV may promote the development of SIL in HIV-infected women through facilitating persistent HPV infection. The association between SIL and HIV infection has led to the inclusion of ICC as a part of the AIDS case definition in 1993 [115], even though the exact relation between the invasive stage of cervical carcinoma and HIV remains uncertain. Furthermore, the addition of ICC to the AIDS case definition emphasised the importance of integrating gynaecological care into medical services for HIV-infected women [115]. However, in cohort studies to date, most HIV-infected women at risk
for low- and high-grade SIL (LSIL and HSIL) did not develop an invasive stage of cancer, because they died of an HIV-related opportunistic infection before such development could occur [116]. In developed countries, effective screening by means of Papanicolaou (Pap) smears and treatment of precursors of ICC also prevent development of ICC. However, in African countries these preventive methods are not routinely available and ICC is there the leading cause of cancer in women [117].

Guidelines for the management of gynaecological disorders are lacking consensus, partly because data are lacking on the incidence and natural history of cervical cancer precursors in HIV-infected women. The US Public Health Service and the Infectious Diseases Society of America recommend two Pap smears in the first year after HIV diagnosis, which may be reduced to yearly screening after two normal test results [118,119]. In Europe, one or two Pap smears are recommended for HIV-infected women every year after HIV diagnosis. If the Pap smears show repeated abnormalities, colposcopy and directed biopsy are indicated. For women who have a cytological diagnosis of HSIL or ICC, colposcopy and directed biopsy are mandatory without delay.

1.2.3.2 Herpes simplex virus (HSV) infection

Two types of herpes simplex virus (HSV) are known. HSV type 1 infection occurs often in childhood and predominantly causes oral-labial lesions (the so-called cold sore), but could also appear in the genital region causing genital lesions. HSV type 2 infection is the major cause of genital herpes worldwide. It is almost exclusively sexually transmitted and leads to painful eruptions on the skin and mucous membranes of the genital area. After primary infection, both types lead to the production of lifelong antibodies. HSV-2 transmissions may occur during asymptomatic shedding of virus by persons who are not aware of their HSV infection. The prevalence of HSV-2 ranges from 8% in pregnant women to 50% in homosexual men and differs by country [120]. The relationship between HSV-2 infection and HIV infection is as described in section 1.2.3 for HIV and STI in general. Particularly a new infection of genital herpes increases the risk of HIV transmission and acquisition compared to recurrent HSV infections [121]. Conversely, genital ulcerations are more severe and more likely to recur in HIV-infected persons than in uninfected persons, especially in those with severe immunosuppression [97]. Also, asymptomatic HSV-2 shedding is more common in HIV-positive than in HIV-negative women, and it increases with increasing immunosuppression [122,123]. Epidemiological studies have shown that in HIV-uninfected women the number of past sexual partners and the number of years of sexual activity are the most important risk factors for HSV-2 prevalence [124-126]. Risk factors for HSV-2 prevalence have been studied extensively in this group, whereas studies among HIV-infected persons are rare.

1.3 The European Study on the Natural History of HIV Infection in Women

Most research presented in this thesis is based on the European Study on the Natural History of HIV infection in Women, more briefly known as the European Women
Chapter 1

Study. This is a prospective cohort study of HIV-infected women with a known interval of HIV infection. For all participants, the interval of HIV seroconversion is retrospectively determined. The aims of the study are 1) to investigate the relationship between HIV infection and cervical lesions, 2) to investigate the natural history of HIV infection in women and its risk factors, and 3) to compare the natural history of HIV infection in women, homosexual men and injecting drug users. From 1993 until 1999, the European Women Study had been co-ordinated by the European Centre for the Epidemiological Monitoring of HIV/AIDS in Saint-Maurice, France. Since 1999, the Municipal Health Service in Amsterdam has been co-ordinating the study. Until date, it was not possible to estimate the median time from HIV infection to AIDS and death, because follow-up time was insufficient. The main reason for this is that HAART, which became widely available in 1996, has substantially delayed progression to AIDS. With continuation of the follow-up, we expect later to obtain sufficient endpoints to answer important questions with respect to HIV infection in women in the era of HAART.

Since 1993, 487 women have been enrolled and followed through 31 centres in 12 European countries: Belgium, Denmark, Finland, France, Greece, Italy, the Netherlands, Norway, Portugal, Spain, Sweden and Switzerland. Enrolment took place from 1993 until January 1998, but follow-up is still ongoing. The follow-up visits are scheduled every six months, and the same anonymous and standardised study protocol is used at each centre to gather information on socio-demographic characteristics, contraceptive use, obstetric and gynaecological history, history of STI, and sexual behaviour. Clinical examination evaluates the stage of HIV infection according to the CDC classification. Blood is drawn to determine markers for disease progression (e.g., lymphocyte counts and viral load) at each study visit. Information on treatments for HIV and other infections is also collected on a routine base. Characteristics of the study population are shown in Table 1. Overall, 70% of the women are heterosexually infected, 50% are living in southern Europe and 10% were born outside Europe, mainly in Africa. The median age at HIV diagnosis is 26 years. All women enter the study HIV-positive, and their interval of seroconversion is determined retrospectively based on the existence of an HIV-negative test less than two years before an HIV-positive test or on a selected period (maximum 2 consecutive years) of reported HIV risk behaviour since 1980, when HIV is assumed to have been introduced in Europe.

Pap smears are taken during gynaecological examination at each visit. Since their interpretation is subject to considerable inter-observer variability, all slides are examined by a single cytologist in Paris. If Pap smears suggest a high-grade lesion, a cervical biopsy is performed to obtain a more precise diagnosis. In case of atypia or low-grade lesion, a cervical biopsy is performed only if the lesions are still present after six months. In case of a persistent lesion (confirmed by biopsy), the therapeutic choice is left to the clinician of the collaborating centre. All gynaecologists involved in the European Women Study make use of the same classification system for colposcopic results. Screening for several STIs takes place at each study visit, but not all centres test by the same system. A positive wet mount is used to diagnose the
presence of vaginal candidiasis and trichomoniasis. Both genital ulcerations and genital warts are diagnosed clinically by means of gynaecological examination. Diagnoses of gonorrhoea are based on gram-stain detection or on a positive culture. Chlamydia trachomatis (Chlamydial) infection is diagnosed on a positive ELISA, PCR/LCR or IF (performed on an endocervical sample), depending on the test available in each centre.

1.4 Multicenter cohort studies among homosexual men

1.4.1 The Tricontinental Seroconverter Study

Although this thesis focuses on HIV infection in women, two studies in gay men are important to the research background. In the Tricontinental Seroconverter Study presented in chapter 2, data were pooled from HIV-positive homosexual men with a known interval of HIV seroconversion participating in five prospective cohort studies on HIV/AIDS in Amsterdam, San Francisco (two), Sydney and Vancouver [96,127-132]. The studies had started in the early 1980s and were ongoing when they began collaboration in 1992. Since each centre of the Tricontinental Seroconverter Study had used its own standardised protocol, previous collected data of each cohort were pooled after making the data compatible, a step that appeared to be highly time-consuming. The aim of the collaboration was to gain knowledge of the natural history of HIV infection and AIDS using information of persons with a known interval of HIV seroconversion. The co-ordination and data management of the study took place in Amsterdam. Funding for the collaboration ended in 1998. The five cohorts are the Vancouver Lymphadenopathy-AIDS Study (the number of men included from Vancouver (n=131)), the Sydney AIDS Prospective Study (n=79), the Amsterdam Cohort Study among homosexual men (n=151), the San Francisco General Hospital Cohort (n=19) and the San Francisco Men’s Health Study (n=46). In total, the Tricontinental Seroconverter Study comprised 426 men. Information on behavioural factors and clinical events was gathered by questionnaires and clinical examinations, respectively. Blood was drawn at each visit to test for virological and immunological markers for HIV disease progression. Follow-up visits were scheduled every 3-12 months, depending on the design of the individual cohort studies.

1.4.2 The combined hepatitis B vaccine trial cohorts of Amsterdam, New York City and San Francisco

The oldest cohort studies related to the natural history of HIV infection comprised HIV-positive homosexual men participating in hepatitis B vaccine trials at the end of the 1970s. These cohorts were established in Amsterdam, New York, and San Francisco. Their storage of blood samples made it possible to test retrospectively for HIV infection, once HIV tests became available. However, these men were followed for reasons related to hepatitis B vaccination and only incidentally to HIV disease progression [3,133]. Described in chapter 3, the study is a typical example of a pooled historical cohort study. As with the study above, its co-ordination took place in Amsterdam. In that city, 3,748 men were screened for hepatitis B markers between 1978 and 1980, and 800 were enrolled in a vaccine efficacy trial. In New York City, approximately 10,000 homosexual men were screened for hepatitis B markers between 1977 and 1978, and 1,090 were enrolled in a vaccine trial. In San
Francisco, 6,704 homosexual men were screened for hepatitis B markers between 1978 and 1980, and 359 were enrolled in a vaccine trial. As part of these vaccine trials, blood was drawn in intervals ranging from 1 to 6 months, and sera were frozen and stored. Beginning in 1983 and 1984, all the men who had participated in these vaccine trials in Amsterdam and San Francisco and 634 of those in New York were invited to participate in the follow-up studies of HIV-1 infection and AIDS. The men included in these new studies were either infected with HIV-1 at entry into the hepatitis B study or documented to have seroconverted during its follow-up. In our pooled analysis, data on 326 seroconverters from Amsterdam, 74 from New York City, and 168 from San Francisco were used. Active follow-up and matches with local and national registries determined the occurrence of AIDS and death.

1.5 Scope of this thesis
This thesis aims to investigate several aspects of the course of HIV infection focusing mainly on women. Initially, however, results from two multicenter studies among homosexual men with a known interval of HIV infection are discussed. In chapter 2, findings of the Tricontinental Seroconverter Study concerning co-factors related to survival following AIDS are investigated. Special attention is given to the time from HIV seroconversion to the development of AIDS as a potential risk factor for post-AIDS survival. In chapter 3, estimates of and cofactors for survival are given, based on homosexual men who participated in hepatitis B vaccine trials in the late 1970s. Estimations of survival time reflect a study extending 18 years from the first HIV seroconversions until 1996, when HAART became widely available.

Subsequently, in chapters 4 to 8, factors related to HIV infection in women are described. The study population in these chapters comprised women included in the European Study on the Natural History of HIV Infection in Women. Chapter 4 covers a study that estimates the impact of HIV diagnosis on the incidence of pregnancy in HIV-infected women. It also addresses the impact of AZT availability to prevent mother-to-child transmission since 1994 and the availability of HAART since 1996, comparing the incidence of pregnancy in calendar periods before and after those pivotal years. In chapter 5, the effect of changes in reproductive hormones during pregnancy and after the menopause on the CD4 decline following HIV seroconversion are discussed, combining data of the European Women Study and the Swiss HIV Cohort Study [134]. The study described in chapter 6 focuses on the influence of HIV-related immunodeficiency and antiretroviral treatment on the occurrence and evolution of SIL in HIV-infected women. In this study, the prevalence, incidence and regression of SIL are estimated. In chapter 7, a study on the incidence of STIs and the effect of HIV-induced immunosuppression on the occurrence of specific STIs in HIV-infected women is described. Finally, the study of risk factors for HSV type 1 and 2 infection in HIV-infected women and the relationship between HSV and HIV infection is presented in chapter 8. The main thesis findings are discussed in chapter 9, with recommendations for further research concerning the course of HIV infection in women.
Table 1. Characteristics at study entry of 487 women included in the European Study on the Natural History of HIV Infection in Women.

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<td>Non-hospital</td>
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<td>17</td>
</tr>
<tr>
<td><strong>Sexual behaviour</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of lifetime partners</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 5</td>
<td>204</td>
<td>42</td>
</tr>
<tr>
<td>6 – 19</td>
<td>169</td>
<td>35</td>
</tr>
<tr>
<td>≥ 20</td>
<td>114</td>
<td>23</td>
</tr>
<tr>
<td>History of other STIs</td>
<td>187</td>
<td>39</td>
</tr>
</tbody>
</table>

1 Transfused, unknown risk.

2 Shown as median and (interquartile range).

3 Based on reported periods of blood transfusion, sharing of injection equipment, or sexual risk behaviour.
References


93. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect 1999;75:3-17.


Chapter 1


