Epidemiological studies of HIV infection in woman
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Chapter 9

General discussion
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This thesis presents seven epidemiological studies based on three different multicenter studies comprising persons with a known interval of HIV seroconversion. Our first two studies were conducted among homosexual men participating in the Tricontinental Seroconverter Study and the combined hepatitis B vaccine trial cohorts of Amsterdam, New York, and San Francisco. The focus of both of our studies is on the natural history of HIV infection, especially the estimation of and risk factors for the median time from HIV seroconversion to AIDS and post-AIDS survival. The other five studies are based on data of the European Study on the Natural History of HIV infection in Women. This study, known briefly as the European Women Study, was established to gain insight in the natural history of HIV infection specifically in women. Several aspects related to the course of HIV infection in women including pregnancies, co-infection with other STI, and the occurrence of cervical lesions are described in this thesis.

9.1 The natural history of HIV infection

Nowadays 46% of the 33.6 million people estimated to be infected with HIV are women, and much concern exists about their rapidly increasing infection rates, but women are still underrepresented in studies. During the two decades of the HIV epidemic, epidemiological cohort studies among homosexual men have extensively investigated the natural history of HIV infection and its associated factors in this population. Estimates of the median time from seroconversion to AIDS vary between 8 and 16 years, and estimates of the median time from AIDS to death vary between 12 and 18 months, dependent on the age of the study population [1,2]. Age at seroconversion was consistently found to be a significant factor related to HIV disease progression. These findings are confirmed by the research on survival following seroconversion and following AIDS, and risk factors for disease progression in homosexual men presented in this thesis (chapter 2 and 3). Among homosexual men participating in the combined hepatitis B vaccine trial cohorts, the annual risk of dying levelled off at 8 years after HIV seroconversion, suggesting that there could be a group of persons that will never progress (chapter 2). However, most subsequent research on non-progression has shown that instead of a group of persons that will never progress, there is a group of very slow progressors representing the right-hand tail of the survival-time distribution [1].

The combined hepatitis B vaccine trial cohorts study is unique in being able to estimate HIV natural history with a follow-up of 18 years following infection before the introduction of HAART, since it started in the late 1970s and early 1980s. One could question whether studies, which were originally set up to study the natural history of HIV infection, are still valuable in the HAART era, because several studies have shown a remarkable increase in survival when comparing survival in calendar periods before and after the introduction of HAART (i.e., before 1996 and since 1996) [3-5]. Others have shown that HAART substantially postponed AIDS and death [6,7]. So strictly speaking, one can no longer investigate the natural history of HIV infection, but rather the course of HIV infection as it is influenced by access to and
compliance with antiretroviral therapy. Nevertheless, in contrast to a randomised controlled trial - the optimal study design to determine the efficacy of and compliance with treatment - observational cohort studies can be very useful at a population level to determine effectiveness of treatment and to assess the long-term effects of treatment. Moreover, to date no large clinical trials are planned that will compare progression to clinical endpoints by various treatment regimens [8]. The impact of newly identified markers for HIV disease progression, such as genetic factors, can be evaluated in cohort studies. Furthermore, natural history studies are valuable for estimating the optimal moment for starting HAART in a given individual. Because of the strict regimen and the serious side effects of this life-long treatment, estimation of the optimal moment to start HAART is important. This moment could be determined by comparing information of a given individual, such as genetic markers and serial measurements of CD4 lymphocyte counts and viral load, with survival patterns and marker paths of persons who participated in cohort studies with a relatively long follow-up period without effective treatment. Cohort studies are also important to estimate the percentage of persons that is receiving HAART, that is willing to start treatment and that has access to treatment. Finally, continuation of natural history cohorts will assist in obtaining unbiased estimates of survival in the era of HAART and investigating risk factors for disease progression in persons treated with HAART. However, they must be conducted not only among homosexual men, but among women and other groups at risk for HIV infection as well.

The absolute number of CD4 lymphocytes in each woman changes during her lifetime probably as a result of changes in levels of reproductive hormones. In HIV-uninfected women, the number of CD4 lymphocytes declines during pregnancy [9]. Postmenopausal women have consistently lower CD4 lymphocyte counts than premenopausal women, whereas pregnant women have lower counts than non-pregnant women (chapter 5). Several studies show that the menstrual cycle is associated with changes in women's viral load as well as CD4 lymphocyte counts occur [10,11]. Gender-related differences in levels of reproductive hormones could also be an explanation for the higher CD4 lymphocyte counts and different viral load levels in women compared to men [12-16]. Recently, one study showed that shortly after HAART was introduced, survival improvement was slower in women than in men [17]. Because no other studies have found differences in HIV disease progression by gender, differences in levels of reproductive hormones and therefore in CD4 lymphocyte counts and viral load may appear to have no function in HIV disease progression. However, studies that have investigated the association between reproductive hormones and CD4 decline are rare, and further research is recommended to clarify this relationship.

9.2 Aspects of HIV infection in women
9.2.1 Pregnancy
Issues related to pregnancy in HIV-infected women have focused predominantly on mother-to-child transmission, with little attention to the potential negative effects of a pregnancy on disease progression in the HIV-infected mother herself. There is great potential for selection bias when comparing HIV disease progression in HIV-
infected women who get pregnant during their infection and those who do not. For example, women with a symptomatic HIV infection may be less likely to become pregnant or more likely to terminate a pregnancy, because they are too ill. Furthermore, the two groups may not be comparable with respect to their stage of HIV infection at study entry. For example, pregnant women may enter when asymptomatic, because they happen to test HIV-positive during routine prenatal care, whereas non-pregnant women may enter later in their disease driven by symptoms related to HIV infection. However, this only counts for cohorts with retrospectively identified seroconverters and do not count for cohorts of HIV negatives who seroconverted during follow-up. Therefore, the effect of pregnancy on disease progression can be adequately answered only in a prospective cohort study that includes women with a known date of seroconversion and that includes information on the reason for study entry [18]. In two prospective studies, no evidence was found for an adverse effect of pregnancy on HIV disease progression after adjustment for time elapsed since infection [19,20], despite a temporary drop in the CD4 lymphocyte counts during pregnancy (chapter 5).

Chapter 4 discusses trends in the incidence of pregnancy and in pregnancy outcomes that were studied before and after HIV diagnosis and by calendar time. Among the subjects, the incidence of pregnancy slightly decreased with time elapsed since infection, but the proportion of pregnancies carried to term increased after 1994, probably due to the availability of AZT to prevent mother-to-child transmission. Future investigations should clarify if this trend will continue with the availability of HAART, which substantially increases life expectancy and optimism. The number of induced abortions was very high in this group of HIV-infected women before as well as after HIV diagnosis, suggesting that a large proportion of pregnancies were unplanned. The high number of abortions and the high incidence of acute STIs other than HIV suggest that unprotected sexual contacts are common. Because pregnancies in HIV-infected women are inextricably bound up with the future health of both mother and child, physicians responsible for the care of HIV-positive women have an important role in family planning, and in encouraging women to plan their pregnancies and to use condoms next to other contraceptives to prevent unplanned pregnancies and the transmission of HIV and other STIs.

9.2.2 Gynaecological disorders and co-infection with other STIs
In HIV-infected women, STIs like chlamydial infection, trichomoniasis and gonorrhoea are high in both prevalence and incidence (chapter 7), but their incidence tends to decrease with ongoing time since HIV infection. STIs like genital lesions, genital warts and genital ulcerations are more likely to occur in immunosuppressed women; they therefore increase after infection by HIV perhaps due to reactivation of HPV and HSV that are latently present in the body (chapter 6, 7 and 8). Risk factors for the presence of HSV-2 antibodies have been frequently studied in the HIV-uninfected population [21,22], but seldom among HIV-infected persons. Our study among HIV-infected women found that the presence of HSV-2 antibodies is strongly related to sexual risk behaviour (chapter 8), which is in line with results of studies among HIV-negative persons [21,22]. Although almost half of
the HIV-infected women had HSV-2 antibodies, only a small proportion mentioned a history of genital herpes, suggesting a high percentage of asymptomatic HSV infections. However, since asymptomatic HSV shedding is common and higher in HIV-infected than in HIV-uninfected persons [23,24], these women may be at higher risk to transmit HSV to sexual partners and new-borns.

SIL are more likely to occur, to progress and to recur after SIL treatment in HIV-infected women than in HIV-uninfected women [25,26]. However, in HIV-infected women of well-screened populations participating in cohort studies, the increased prevalence of SIL has not led to a substantial increase in the incidence of invasive cervical carcinoma (ICC), which was added as an AIDS-defining event to the AIDS case definition in 1993. Cross-sectional studies have shown an increase in cervical cancer in HIV-infected compared to HIV-uninfected women, but in this type of study causality can not be determined and the higher prevalence might be explained by selection bias reflecting social and cultural differences between HIV-negatives and HIV-positives [27,28]. Since HAART became generally available in 1996, the immune status of HIV-infected persons treated with HAART has substantially improved. The effect of this improvement on cervical lesions and HPV infections is highly relevant for the management of gynaecological diseases. In our study (chapter 6), the association between HIV-related immunodeficiency and the occurrence of SIL remained statistically significant after adjustment for HPV detection in cervical samples. It could be that by decreasing the control of HPV infection, immunodeficiency may increase the duration of HPV infection and/or may allow HPV to replicate to higher levels of HPV load, increasing its risk of oncogenic progression. Taking into account these results, one can imagine two possible scenarios for the effect of HAART on SIL. (1) If women begin HAART after developing HSIL and their immune response to HPV is restored, then one might expect HPV levels to decrease, HSIL to regress, and the incidence of cervical cancer to decrease. (2) Women will live longer due to HAART but if HAART itself does not have an impact on the immune response to HPV, women with HSIL might then have the opportunity to progress to ICC, resulting in an increased incidence of ICC. Since most cases of HSIL do not regress spontaneously even in HIV-uninfected women, the second scenario seems more likely [29]. One prospective study showed that in 49 women receiving HAART, HAART reduced the prevalence of SIL despite failing in most of these cases to clear HPV infection [30]. The women with regression of SIL due to HAART had a higher increase in absolute CD4 lymphocyte counts, suggesting that host immunological factors play a role in the development of SIL. However, the study population of this study was small and one did not compare the regression of SIL of treated and untreated women. In chapter 6, the incidence of SIL was lower (although not to a statistically significant degree) for women who received antiretroviral therapy (at least one drug) than for women who did not receive antiretroviral therapy, after adjustment for differences in CD4 lymphocyte counts. This finding suggests that HIV infection itself is an independent factor in the development of SIL.

To conclude, the risk of HIV transmission is increased by co-infection with other STI. HIV-infected women co-infected with STI are therefore an important target group for
strategies to prevent HIV transmission in the heterosexual population. Regular screening and early treatment of gynaecological disorders are necessary beside promotion of condom use.

9.3 Future study objectives
In the HAART era, cohort studies remain important to monitor the course of HIV infection and to evaluate marker paths from the pre-HAART era for the optimal moment to initiate HAART. Despite differences in the markers for HIV disease progression between men and women, treatment regimens for HIV-infected persons are based predominantly on knowledge gained through studies among homosexual men. Therefore, more attention should be paid to gender differences in markers, and women should be adequately represented in cohort studies and clinical trials. Continuation of the European Study on the Natural History of HIV Infection in Women is very important. Until now, follow-up was insufficient to estimate survival time from seroconversion to AIDS and survival following AIDS in this group of predominantly heterosexually infected women. But with ongoing follow-up, it will be possible to estimate these survival times and to compare them with estimates of survival in men both before and after the introduction of HAART. Furthermore, continuation of follow-up will also elucidate aspects related of HIV infection specific to women, such as pregnancy, co-infection with other STIs and SIL occurrence, and how trends in the incidence of pregnancy and pregnancy outcomes are affected by the availability of HAART.

Another aspect to study would be the association between HIV-1 subtype and disease progression in women. In Europe, most of the HIV-1 infections in homosexual men and injecting drug users are subtype B, whereas in AIDS-endemic countries, most infections in both men and women are non-B. The association between HIV-1 subtypes and disease progression has been studied only in small groups with conflicting results. One study found that women infected with non-A subtypes had a shorter progression towards AIDS than women infected with subtype A [31]. However, two other studies found no differences in the CD4 decline between persons infected with B and non-B subtypes [32] or in progression rates between persons with subtype C and B infections [33]. Because 13% of the women participating in the European Women Study had a sexual partner from an AIDS-endemic region at the time they seroconverted for HIV and 12% were themselves from an endemic region, this study has the potential to advance this important objective without bias due to different social circumstances and study designs.

As mentioned previously, the role of HIV and HAART in the SIL occurrence, prognosis, response to treatment, and recurrence is another subject for further investigation. Since HAART became generally available in 1996, the immune-status and life expectancy of HIV-infected persons receiving this therapy have substantially improved. Whether this improvement has resulted in regression of cervical lesions has not yet been clarified, but such knowledge is highly relevant for the management of gynaecological diseases. The European Women Study is one of the few studies worldwide that includes women with a known interval of seroconversion and that has
longitudinal gynaecological data (i.e. results of Pap smears, biopsies and colposcopy) with the potential to describe the incidence and prognosis of cervical lesions in HIV-infected women receiving HAART, adjusted for time since infection. Since other studies in this field lack data either on HIV seroconversion or on gynaecological measurements, the European Women Study represents a unique database with high relevance for reviewing SIL treatment guidelines and developing treatment recommendations for these cervical lesions in HIV-infected women.

Given these unanswered questions, the lack of cohort studies among women and the fact that women now comprise 46% of all HIV-infected persons, it is difficult to understand that no Dutch or European funds have been made available to continue this unique cohort study.
References


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