Epidemiological studies of HIV infection in woman
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Citation for published version (APA):

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Download date: 08 Dec 2018
Summary
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During the two decades of the HIV epidemic, epidemiological cohort studies extensively investigated the natural history of HIV infection and its associated factors (chapter 1). Most of these studies are conducted among HIV-infected homosexual men. It cannot be assumed that the course of HIV infection will be the same in men and women. For example, gender differences exist in the two most important markers of HIV disease progression, CD4 lymphocyte counts and HIV RNA levels. However, to date no gender differences are observed in HIV progression rates. In this thesis two studies on progression of HIV infection in homosexual men and five studies on aspects related to the course of HIV infection in women are described.

Data from the Tricontinental Seroconverter Study were used to investigate the impact of the time from seroconversion to AIDS and other risk factors for survival following AIDS among homosexual men (chapter 2). These data indicated that survival following AIDS can be predicted by information obtained at the time of AIDS diagnosis, like the age at diagnosis, the type of AIDS diagnosis and the CD4 lymphocyte count at the time of AIDS. The time from seroconversion to AIDS did not affect survival after AIDS. Thus for persons who do not receive HAART, AIDS seems a significant point in progression to death, and not just a floating point between infection and death affected by prior factors. However, AIDS could be a floating point for patients receiving HAART dependent on compliance with therapy.

The study that combined hepatitis B vaccine trial cohorts of homosexual men in Amsterdam, New York and San Francisco is one of the oldest cohort studies of homosexual men with a known interval of seroconversion. Therefore, the natural history with a follow-up of 18 years before the widespread use of HAART could be estimated (chapter 3). The median survival time from seroconversion to death was 12.1 years. The annual risk of dying increased at a constant rate until 8 years after seroconversion and then levelled off, suggesting a group of HIV-infected persons that is relatively resistant to infection.

The studies among women (chapter 4 to 8) are based on the European Study on the Natural History of HIV Infection in Women, which is one of the few cohort studies that includes data of heterosexually infected women with a known interval of seroconversion. This study comprises 487 women that have been followed in 31 centres in twelve European countries since 1993.

To investigate whether reproductive decision making is affected by knowledge of HIV serostatus, the incidence of pregnancy and outcomes of pregnancies before and after HIV diagnosis was estimated (chapter 4). The incidence of pregnancies decreased with HIV disease progression, independent of age. Pregnancies after HIV diagnosis were independently associated with marital status and geographic region. This suggests that reproductive decision-making after HIV diagnosis is related to social and cultural values. The number of induced abortions among the pregnant women was 42% before HIV diagnosis and increased after HIV diagnosis to 53%.
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Single women and women with multiple partners were at an increased risk of an induced abortion. Although pregnancy rates did not increase, the percentage of pregnancies carried to term increased significantly after 1994, the year in which zidovudine was introduced as effective drug to prevent mother-to-child transmission.

To study the effect of levels of reproductive hormones indirectly, we investigated the impact of pregnancy and menopause on CD4 lymphocyte counts in HIV-infected women (chapter 5). Pregnancy had only a temporary effect on the CD4 decline. Postmenopausal women had lower CD4 lymphocyte counts than premenopausal women shortly after infection and the CD4 slope was similar for both groups. This means that postmenopausal women continue to have lower CD4 lymphocyte counts with ongoing HIV infection. Differences between pre- and postmenopausal women might be explained by changes in the level of reproductive hormones after the menopause and could be an explanation for described gender differences in CD4 lymphocyte counts.

In HIV-infected women, severe immunodeficiency was associated with a high prevalence of SIL, a high incidence of SIL, a low regression rate from low-grade SIL, and a high rate of recurrence/persistence after treatment of high-grade SIL (chapter 6). These associations were independent of HPV detection in cervical samples. After adjustment for CD4 lymphocyte counts, the incidence of SIL appeared to be lower in women who received antiretroviral therapy than in women who did not receive antiretroviral therapy. This might suggest that HIV itself is an independent factor in the development of SIL.

Prevalence and incidence of STI in HIV-infected women in relation to time from infection and sexual behaviour are described in chapter 7. The occurrence of genital warts, genital ulcerations and vaginal candidiasis was high and, although women knew their serostatus, acute STI (i.e., chlamydia, gonorrhoea, and trichomoniasis) were frequently acquired. Results suggest that the risk of acute STI decreases and the risk of genital warts and genital ulcerations increases with ongoing time since seroconversion. Since transmission of HIV is enhanced by co-infection with STI and vice versa, regular gynaecological examinations next to prevention measures are recommended for HIV-infected women to reduce morbidity and further HIV transmission.

The results described in chapter 8 showed that the prevalence of HSV-1 and HSV-2 antibodies is high in HIV-infected women. The prevalence of HSV-1 antibodies differed by geographic region, being more common in women living in southern Europe than women living in northern and central Europe. HSV-2 infection was strongly related, whereas HSV-1 infection appeared unrelated to sexual behaviour in HIV-infected women. The risk for recurrent genital ulcerations was the highest in immunosuppressed HIV-infected women, which is in line with the results described in chapter 7.
To conclude, studies described in this thesis have contributed to the knowledge of the natural history of HIV infection and aspects related to HIV infection in women. Although HAART drastically changed the natural history of HIV infection, cohort studies remain important to assess the long-term effects of treatment, to evaluate the impact of newly identified markers, to estimate the optimal moment to start therapy and to obtain unbiased estimates of survival times in persons treated with HAART (chapter 9). Continuation of the European Study on the Natural History of HIV Infection in Women will give unique opportunities to gain more insight in HIV disease progression in women and potential risk factors such as HIV-1 subtypes, pregnancies and other STI. Besides this, these data are valuable for investigating the association between HIV infection and the occurrence and progression of cervical lesions in women receiving HAART as guidelines for SIL treatment in HIV-infected women might need to be revised in the era of HAART. 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.