Markers of HIV-1 infection and its pathogenesis
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Citation for published version (APA):

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Chapter 9

Summary
1) Introduction
After the introduction and the historic overview of the different study groups and logistics of the Amsterdam cohort study amongst homosexual men (ACS), a short summary is given of the five studies presented in this thesis.

2) The Amsterdam cohort study
The Amsterdam Cohort Study of Human Immunodeficiency virus (HIV-1) infection and AIDS amongst homosexual men (ACS) was started in 1984. This was shortly followed by the Amsterdam cohort study amongst intravenous drugs users in 1985. The multidisciplinary approach encompassing epidemiology, social science, virology, immunology and clinical medicine has significantly contributed to the knowledge and understanding of the various aspects of HIV-1 infection and AIDS. Four major fields of interest were explored. The first was to study the prevalence and incidence of HIV-1 infection and AIDS. This was followed by studies designed to discover and describe the natural course of HIV-1 infection and AIDS. The third point of interest was to examine various risk factors and to monitor changes in sexual behaviour over time. Finally, several intervention studies were performed to investigate the antiretroviral effects and the emergence of resistance to several types of treatment.

3) Blind T cell homeostasis
Recently, the hypothesis of the blind T cell homeostasis was proposed. This was based on the observation that the level of circulating T cells is maintained without regard to the phenotype of T cell subsets. It was postulated that in order to keep the level of total T lymphocytes constant, the progressively declining number of CD4\(^+\) T cells is compensated for by an increased number of CD8\(^+\) T cells. In the study presented, we have investigated the presence of T cell homeostasis in the ACS and whether homeostatic failure, associated with downwards inflection of the total T cells, was related to the switch from a non syncytium-inducing (NSI) to syncytium-inducing (SI) virus phenotype.
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As predicted by the homeostasis concept, indications were found of an acute downward inflection of the total T cell count two year before the onset of AIDS. Furthermore, we found that the times of SI switch and IP were highly correlated.

In summary, these results convincingly support the concept of blind T cell homeostasis and shown that the SI virus phenotype plays an important role in the failure of T cell homeostasis.

4) Delayed-type hypersensitivity skin testing
Skin test anergy (the inability to induce a skin reaction after intra-cutaneous administration of so-called recall antigens) is seen in 20-30% of the HIV-1 infected individuals. In the study presented in chapter 4 we investigated the relationship between skin test anergy and the outcomes of various immunological and virological laboratory assays used in the daily routine of the ACS. For the evaluation of skin test anergy we used the commercially available Multitest CMI applicator.

In this study, a strong association was found between decreased T cell reactivity in vitro and skin test anergy. Based on the findings presented in this study we concluded that the used T cell reactivity tests can be considered as an accurate reflection of the cellular-mediated immunity.

5) Mannose-binding lectin
In chapter 5 a study is presented in which the morbidity and mortality of HIV infected individuals is studied in relation to Mannose-Binding Lectin (MBL) polymorphism. MBL is a serum protein that plays a central role in the opsonisation, phagocytosis and activation of the complement cascade. In this study, indications were found of a relationship between a mutation in the gene encoding for MBL and a slightly delayed onset of AIDS. In addition, this mutation also appeared to be protective against developing Kaposi’s sarcoma (KS). Finally, we speculate that these findings are suggestive of the fact that, next to the traditional routes such as the CD4 cell membrane receptor or by co-receptors such as
CCR5 and CXCR4, HIV is also able to infect host cells through complement activation.

6) Early weight loss in asymptomatic HIV infected individuals
In advanced stage HIV-1 infected individuals, severe weight loss often heralds the beginning of a more aggressive course of infection, mostly leading to AIDS and/or death. The aim of the study presented in chapter six of this thesis, however, was to investigate whether there were indications of early weight loss, and if so, whether those early pre-AIDS weight losses were predictive of getting AIDS.

We found amongst persons who developed AIDS a biphasic weight pattern. After a relatively long period in which the body weight hardly changed, there was a sudden decline six months before AIDS. We speculated that, due to the close correlation between weight maintenance and HIV RNA, this rapid weight decline six months before AIDS is probably caused by an increase of HIV RNA load shortly before AIDS.

7) Sun light exposure and progression of HIV-1 infection.
It has been known for a long time that exposure to sunlight, and especially to ultraviolet radiation (UVB), can suppress cellular immunity.

Furthermore, it can also cause the activation of some viruses such as the herpes simplex type I, sometimes resulting in a herpes labialis (cold sores). Additionally, there are some case-reports describing a more aggressive course of disease in advanced HIV infected individuals after exposure to high doses of UVB. Because of this many clinics discourage HIV infected individuals from submitting themselves to high doses of UVB exposure during holidays.

The aim of the final study presented in this thesis therefore was to investigate whether we could find indications that exposure to sunlight and especially UVB was indeed harmful to HIV infected individuals. By means of a questionnaire, we assessed each person’s exposure to UVB over the previous two years. From this, two exposure measurements were calculated: a total cumulative exposure measure, comprising of the total amount of received UVB
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and a short-term cumulative measure, comprising the amount UVB received per period. Subsequently, those UVB exposures were compared with the outcomes of three different immunological markers (CD4+ T cell count, CD4/CD8 ratio and T cell reactivity after stimulation with CD3 antibodies) that had been assessed in the same period. In neither of the UVB analyses, using the total and short-term exposure calculations, indication could be found of an interaction between UVB exposure and cellular immunity.