Markers of HIV-1 infection and its pathogenesis
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Chapter 1

Introduction and the outline of this thesis
Introduction

In the MMWR of June 1981 an unusual cluster was described of 5 young homosexual men with Pneumocystis carinii pneumonia (PCP) who had been admitted to three different hospitals in Los Angeles, California. In the following issue of the MMWR, July 1981, it was reported that 26 homosexual men had been diagnosed with a very uncommon malignancy, called Kaposi's sarcoma (KS). All KS cases had been diagnosed during the previous 30 months. A review of the New York University coordinated Cancer Registry for KS in men under the age of 50 revealed only three previous cases in the period from 1961 until 1979. Therefore, to find so many cases of KS among young homosexual men within a thirty month period was considered very unusual. In most of the cases, white homo- or bisexual men were involved. As well as the PCP and KS cases, there was also a substantial number of patients diagnosed with other opportunistic infections such as Candidiasis and Mycobacterium-avium-intracellularare. It was suggested therefore that an immune dysfunction had to be the cause. This hypothesis was supported by the fact that a dose-response relationship was found in these patients between the severity of the clinical situation and the depression of the T-lymphocyte helper-to-suppressor ratio. In July 1982 it was reported that the acquired immune-deficiency disease (AIDS) had spread to other risk groups as well. The highest proportion of cases was still seen among homo-and bisexual men (73%), followed by intravenous drug users (17%), Haitian immigrants to the USA (3%), haemophiliacs (1%) and receivers of blood transfusions (1%). Although the aetiology of AIDS was still unknown, epidemiological evidence suggested that AIDS was caused by an infectious agent transmitted sexually and through exposure to blood or blood products. In 1983 the Human immunodeficiency virus (HIV) was isolated from peripheral blood T cell lymphocytes from patients with AIDS. Soon after that, antibody tests for HIV became available. This enabled the physician to identify persons.
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infected with HIV and the epidemiologist to perform sero-epidemiological studies. After the major routes of transmission had been established, attention turned to investigating the natural history of the disease and the identification of causal determinants and markers of progression. Since the discovery of HIV, great efforts have been made to understand the mechanism of interference with human immunity and the disturbance of the viral life cycle by therapeutic interventions. With the introduction of zidovudine (AZT) in 1986 13, it became possible to delay the progression of the disease for a period of at least two years 14. In addition, prophylactic treatment of opportunistic infections resulted in a prolonged incubation time from the moment of HIV-1 infection until clinical AIDS 15-19

At present, HIV has become pandemic. The total number of HIV infected persons is estimated to be 33 million (UNAIDS update) 20, of whom more than 60% are living in sub-Saharan Africa 21. In those countries, the impact of AIDS on the general population is devastating. In a recent survey, for example, HIV prevalence among a sub-population of pregnant women in Southern Africa was 45% 21.

Furthermore, sub-Saharan Africa is also the region in which 80% of all AIDS deaths occurred in 1998 20. In the Western world, however, which can afford the highly expensive antiretroviral therapy, both the morbidity and mortality of persons infected with HIV have dramatically decreased 22-24. In Amsterdam, for instance, between 1996 and 1997 the incidence of AIDS dropped 33% 25.

1.2 The scope of this thesis

This thesis addresses several topics concerned with the natural history of HIV-1 infection among homosexual men. The second chapter gives an overview of the history of the Amsterdam cohort study on HIV/AIDS among homosexual men (ACS). This study was started in 1984 as a collaboration of five different research institutes in Amsterdam. All further chapters in this thesis describe studies that have been performed in the scope of the Amsterdam cohort study.
Although failure of Blind T cell homeostasis is established as one of the major mechanisms involved in progression to AIDS, this concept has never been tested in any cohort other than the Multicenter AIDS Cohort Study (MACS). By applying the same criteria and methods used in the MACS to the ACS data, we were able to investigate the validity of the blind T cell homeostasis concept. Moreover, because HIV-1 phenotype had been assessed on all ACS participants every three months since the beginning of 1984, we were also able to investigate whether there was a relationship between the moment of non-syncytium-inducing to syncytium-inducing virus switch (NSI/SI) in peripheral blood and the moment of failure of Blind T cell homeostasis. The results of this study are presented in chapter three.

Depending on the number of CD4+ T cell counts, delayed-type hypersensitivity skin test anergy (DTHA) is seen in 10-75% of the HIV infected cases. The prognostic significance of DTHA has also been recognised in the Walter Reed classification, in which it was an independent indicator for the progression to disease. In chapter four the relation was investigated between DTHA and various established markers, used for monitoring the progression of HIV-1 infection.

In a recent study, an association was found between a shorter survival after AIDS and a mutation in the gene encoding for Mannose-Binding Lectin (MBL). Serum MBL is a liver-synthesised protein, which plays a role in first-line defence immunity. Surprisingly, no association was found between the mutation and the time from the moment of HIV seroconversion to AIDS. This however could be explained by the fact that the moment of HIV-1 seroconversion was unknown in this study. The aim of the fifth study described in this thesis was therefore to examine the association between MBL polymorphism and progression to AIDS and death in the seroconverters cohort.

The wasting syndrome, which is defined as an unintentional weight loss of more than 10%, is one of the most devastating symptoms of advanced HIV-1 infection. Because it is unclear whether AIDS is preceded by gradual weight loss, pre-AIDS changes were assessed in...
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asymptomatic HIV-infected men. We used these findings to determine whether early weight loss is predictive for the progression to AIDS. This study is presented in chapter six.

From the Ultraviolet radiation B (UVB) literature, it is evident that UVB can have negative systemic effects on a great number of the human parameters of immunity, and that it is capable of reactivating HIV replication in vitro. However, whether these findings are relevant to the medical treatment and daily life of an HIV infected individual is not yet clear. The aim of the study presented in chapter seven therefore was to investigate the association between UVB exposure – assessed by a questionnaire – and various immunological established markers of progression. Finally, in chapter eight, the results of the studies are discussed in comparison to the results of other studies.
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