Epidemiological studies among injecting drug users infected with HIV: highly active antiretroviral therapy, tuberculosis, hepatitis C, immunology
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Citation for published version (APA):

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Summary

This thesis presents research on injecting drug users (IDU) who are infected with the human immunodeficiency virus (HIV). All but one of the studies were conducted on pooled data from cohorts in 7 cities or regions in Europe participating in the European Seroconverter Study among IDU. Commonly, individuals do not know when they were infected with HIV. Notably, all IDU in the European Seroconverter Study had a known date of seronegative and seropositive HIV test (seroconverters) thus allowing for accounting for the duration of HIV infection in statistical analyses. Besides studying the progression of HIV infection and the importance of the immune system in IDU, also aspects of tuberculosis and hepatitis C infection, two infections that are common in this group, were investigated.

HIV disease progression since highly active antiretroviral therapy (HAART)

Initial effect of HAART limited

Shortly after highly active antiretroviral therapy (HAART) became available in 1996, evidence came that HIV-positive injecting drug users benefited less from this therapy than other risk groups. Data from the European Seroconverter Study were used to study the impact of the availability of HAART on the progression rates to AIDS and death among injecting drug users (chapters 2 and 3). In the first one and a half years of HAART availability (1996-1997) the risk of AIDS and death for injecting drug users decreased by 28% and 36% respectively. The initial 36% survival benefit was less than the decrease that had been reported for other risk groups (50%-64%). Notably, 3 years prior to the availability of HAART, the risk of AIDS had tended to increase among IDU (23%), probably due to the extension of the AIDS definition in 1993 which came to include 3 extra diseases of which 2 mainly affected IDU (pulmonary tuberculosis and recurrent pneumonia). When ignoring the extension the estimated risk reduction of AIDS in time of HAART altered only minimally, therefore correcting for the 1993 extension of the AIDS definition is apparently not necessary.

The recent years

A later study among the same IDU including longer follow-up showed that with ongoing HAART availability the risk of AIDS and death has continued to decrease further (chapter 3). By 2000-2001 the risk of AIDS was reduced by 65% and for death by 75% compared to the pre-HAART era. These reductions however, remain of a lesser magnitude than the reductions among other groups in Europe in the same time period (87%-91%). Differences in progression rates in the HAART era by geographic region have not been studied previously. Factors that may be of importance regarding HIV disease progression in the face of HAART availability, such as drug adherence, co-infection with hepatitis B and C, and patient management and the organisation of care for HIV-infected drug users in general may differ across Europe. However, the progression rates to AIDS showed little geographical variation although there was more variation in the risk of death. All cause mortality was increased in IDU in Glasgow and the risk of non-natural deaths was lowest in IDU in the Valencian region of Spain. The timing at which HAART is initiated clearly differed across Europe, with IDU in Amsterdam, Edinburgh, and Innsbruck starting HAART at significantly lower CD4+ T cell counts (representing more advanced immune deficiency) than IDU in Paris, Geneva, Glasgow and the Valencian region. However this did not lead to apparent variations in the subsequent short-term immune response (chapter 3).
Tuberculosis (TB)

TB risk varies with the duration of HIV infection

As it was unknown whether the risk of active tuberculosis disease varied with the length of time that individuals are infected with HIV this issue was investigated in chapter 4. It appeared that in IDU the risk of tuberculosis varied with the duration of HIV infection, independently of the state of the immune system. The risk of tuberculosis was increased relatively early in HIV infection (year 4 to 6) and also later (after year 9) with probably a relatively silent period in the years between. This pattern was not attributable to variations with time since seroconversion in the incidence of pulmonary tuberculosis and extra pulmonary tuberculosis. We hypothesized that maybe reactivation of latent M. Tuberculosis infection occurs earlier in HIV infection, whilst late in HIV infection (after 9 years in our data), susceptibility to new tuberculosis infection is increased.

Geographic distribution: TB risk unexpectedly high in Amsterdam

The prevalence of tuberculosis is known to differ by geographic region and as expected, IDU in Southern Europe showed a substantially higher risk of tuberculosis than IDU in Northern and Central Europe. However, Amsterdam formed an exception for Northern Europe, with very high incidence rates (chapter 4). A good tuberculosis case-finding system but no prophylaxis policy in Amsterdam may in part explain the high incidence rates. Furthermore the Amsterdam cohort may have attracted a more marginalized group at higher risk of TB than the IDU in the other cities.

Hepatitis C

High degree of hepatitis C virus exchange across Europe

The spread of hepatitis C virus (HCV) among HIV co-infected IDU is described in chapter 5. The great level of diversity and lack of geographical clustering of HCV strains revealed that HCV exchange between European IDU populations has occurred on a large scale. Also, to date, HCV virus strains are less region specific than HIV strains. This may be due to the fact that HCV has been present for longer and has had more time than HIV to spread, but perhaps HCV is also exchanged at a greater intensity between IDU populations than HIV.

HCV Genotype 4: a recent introduction?

In contrast to genotypes 1, 2, and 3, HCV Genotype 4 is not very common in northern and central Europe and is seen mostly in individuals with a foreign background and increasingly in IDU. The percentage of genotype 4 was relatively high among the studied IDU (ranging from 7% in Northern Europe to 24% in Southern Europe) and consisted mainly of subtype 4d. The evolutionary distances within this subtype were lower, suggesting that this subtype may have entered the European IDU population only relatively recently (chapter 5).

Does carrying multiple HCV genotypes accelerate HIV disease progression?

Due to contradicting studies, it is still not clear whether individuals infected with both HIV and HCV will develop AIDS and die at a faster rate than those with HIV infection alone. The different HCV genotypes that are involved may play a role in this issue. In chapter 6 it is shown that compared to other genotypes progression to low CD4+ T cell counts is enhanced in IDU with HCV genotype 1 infection but that both clinical and immunologic progression are especially faster in individuals whose HCV infection involves more than one HCV genotype. Furthermore, the effect of HCV genotype on HIV progression was greater in the pre-HAART era, suggesting that the effectiveness of HAART may diminish the effect of HCV genotype on HIV disease
progression. However, the small numbers in this study and the unclarity as to what comes first (do multiple HCV types make HIV-infected individuals sicker or are sicker individuals more susceptible for multiple HCV infections?) make further research on this topic necessary.

**Immune status**

*Already important prior to HIV infection*

Not much is known about the extent to which the immune status in healthy individuals before HIV infection determines subsequent HIV disease course. Stored viable cells that were obtained prior to HIV infection allowed for the unique opportunity to study this issue among HIV-positive drug users. The findings illustrated that a better immune status prior to HIV infection does indeed affect the disease course after HIV seroconversion (chapter 7):

*The more CD4+ T cells the better*

HIV infection is characterized by the gradual erosion of the immune system owing to a loss of CD4+ T lymphocyte cells which are an important component of the immune system. IDU starting off with higher numbers of CD4+ T cells prior to HIV infection maintained higher levels of these cells throughout HIV infection.

*Are immune systems burdened in the past at a disadvantage?*

The T-cell receptor excision circle (TREC) content of CD4+ T cells is probably a marker which better than CD4+ T cells reflects inter-individual differences in the number of infections experienced throughout life and differences in genetic predisposition to immune stimulation in response to infections (with higher TREC content reflecting an assumably lower historical burden of the immune system). Drug users with the highest TREC content prior to HIV infection displayed significantly slower erosion of their immune system during HIV infection.