Epidemiological studies among injecting drug users infected with HIV: highly active antiretroviral therapy, tuberculosis, hepatitis C, immunology
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Chapter 1

General introduction
Bevoorbeeld iemand zit heerlijk te roken.

Maisha van Asten, 2001
General Introduction

At present, Sub Saharan Africa is the region that is hit hardest by the human immunodeficiency virus (HIV) epidemic, with prevalence rates of 30-40% in some countries [1]. Although the numbers stand in no comparison to those in Sub Saharan Africa, also in the western world large groups live with HIV infection. By 2003 more than half a million HIV-infected individuals were reported in western Europe and an estimated 21 thousand infections continued to occur in this region in 2004 [2]. Besides homosexual men and patients with hemophilia, injecting drug users (IDU) were a hard hit group at the beginning of the epidemic in the early 1980’s. For this thesis aspects of the course of HIV infection in injecting drug users in Western Europe were studied. Besides studying the impact of the availability of new anti-HIV drugs on HIV disease course, two other infections typically seen in HIV-infected drug users, Hepatitis C virus and tuberculosis, and the effect of pre-infection immune status on subsequent HIV disease progression were studied.

Prevalence of injecting drug use

Based on the limited available data, it was estimated that by the end of 2003 there were approximately 13.2 million IDU worldwide which amounts to 0.3% of the total adult population. An estimated 1 to 1.4 million IDU live in Western Europe, and the proportion of injecting drug users among adults is highest in Spain, Malta, Albania and Greece (0.70%-1.06% of the adult population). In the Netherlands, this proportion is estimated at 0.04% or approximately 3-5 thousand individuals aged 15-64 [3].

Prevalence of HIV infection in IDU

Global prevalence

Drug users are a major risk group for HIV infection because of the sharing of needles and other injection equipment. It has been estimated that globally, approximately 10% of HIV/AIDS cases are attributable to injecting drug use [3]. IDU represent the most prevalent group with HIV infection in several eastern and southern Asian countries (Malaysia, China and Vietnam) and in central and eastern Europe (former Soviet Union). An estimated 66%-82% of all HIV/AIDS cases in these countries were attributable to injecting drug use in 1999 or thereafter [3]. The severe HIV epidemic among injecting drug users (IDU) in most countries of the former Soviet Union is a very recent one: after a few small outbreaks in the nineties, two very large outbreaks were identified in the Russian Federation in 1999 and the situation has worsened since [4]. Also the Baltic States and North Africa have HIV epidemics driven by injecting drug use. HIV prevalence among IDU varies strongly between countries but also within countries. Many countries have at least one report of high (>20%) HIV prevalence in IDU in the capital city or other major urban areas. Information on HIV prevalence in IDU is not available from many countries in North Africa, the Middle East, sub-Saharan Africa, Latin America and the Caribbean [3].

Prevalence in Western Europe

After its introduction in the gay community in Europe, HIV spread rapidly among injecting drug users across Western Europe and the prevalence became especially high among drug users in southern European countries such as Italy and Spain and still today, injecting drug users remain a large risk group in these countries. In Portugal, a southern European country with a relatively late HIV epidemic, injecting drug use accounted for almost 50% of all HIV infections in 2002 [1]. In recent years increasing trends in HIV diagnoses have been reported in 12 western European countries but mostly among risk groups other than injecting drug users. The number of new HIV
diagnoses among injecting drugs users in western Europe peaked in the late 1980’s and has gradually declined more recently from over 600 new infections per year in the mid 1990’s to a little over 500 new cases in 2002 [5]. The total number of drug users currently infected with HIV in Western Europe is not known, but over 100,000 IDU with AIDS were reported between 1999 and 2003.

**HIV infection: differences between IDU and other risk groups**

Regarding HIV infection, there are differences between IDU and other HIV-infected groups. IDU are mainly infected due to unsafe injecting whereas the transmission routes among other groups comprise unsafe sex, mother to child (vertical transmission), and the receipt of blood and blood products. Kaposi sarcoma, a very rare disease in northern Europe and typically diagnosed in HIV-infected homosexual men as an early AIDS defining event, mirroring the higher prevalence of human herpes virus type 8 in these men, is rarely seen in IDU [6]. Tuberculosis and recurrent pneumonia, two diseases which were added to the list of AIDS defining diseases in 1993, are more common among HIV-infected IDU than among other HIV-infected groups in the western world [7-9]. Also, at the biological level HIV does not evolve in entirely the same pattern in IDU as in homosexual men: the appearance of the more aggressive syncytia inducing HIV variants being more common in the latter group [10]. Furthermore, besides the use of drugs itself, IDU differ largely in lifestyle factors from other HIV risk groups. They are more likely to have a chaotic lifestyle, a substandard level of hygiene and to be homeless [11,12]. Despite all these differences between risk groups, the time from HIV infection to death or AIDS did not clearly differ among risk groups prior to the introduction of highly active antiretroviral therapy (HAART) when adjusted for age [13,14]. Variations in the spectrum of AIDS defining diseases and the larger proportion of HIV-infected IDU dying prior to the development of an AIDS defining disease were the only clear differences with respect to HIV progression in IDU compared to other risk groups in the past, prior to the general availability of highly active antiretroviral therapy (HAART) [15-17].

**Drug users and anti-HIV therapy**

In 1996 highly active antiretroviral therapy (HAART) became widely available. Although not a cure for HIV, these were the first combinations of drugs which slowed disease progression, causing dramatic declines in the incidence of AIDS defining diseases and mortality [18-20]. However, where disease progression did not differ between risk groups prior to HAART availability, IDU showed less improvements than other risk groups since its availability [20] which was due to a reduced access to HAART and lower treatment adherence rates in this group. Continued drug use reduces the likelihood of being prescribed antiretroviral treatment [21-23] but also patient refusal rates of antiretroviral therapy are higher among IDU [24]. A patient’s limited ability to keep appointments, alcoholism and homelessness are factors which deter providers from prescribing HAART as the regimens need to be strictly adhered to. Suboptimal; therapy is unable to suppress viral replication and can lead to drug resistance and the limitation of future treatment options [25]. Regimens used to be complicated with many different pills, strict time schedules for medication intake and different meal specifications for different drugs, although more recently simplified treatment regimens have been developed [25]. Suboptimal; adherence is a strong predictor of a decreased response to HAART and treatment failure [26]. Very high levels of adherence are necessary to achieve virologic suppression of HIV: studies vary, reporting minimal necessary levels of adherence of 80% but even up to >95% [26], and the immunologic and virologic response to treatment (i.e. the increase in CD4+ T cells and decrease of viral load) has been demonstrated to be lower among groups of IDU than among non-IDU [27-30]. However,
suboptimal adherence not only occurs among drug users. In general individuals who are younger, suffer from depression, with a self-perceived lack of social support, or are homeless, display a poorer adherence at similar levels as drug users [31]. Among drug users in the USA a suboptimal; virologic response is most likely among active injectors whilst former drug users may have similar response rates as non-drug users [32]. For active drug users the attendance of a methadone maintenance therapy program is associated with the receipt of HAART and an improved adherence [11]. For IDU, many factors play a role in the problem of not achieving a sufficient level of adherence. These include intolerable side effects caused by HAART (including a perceived decreased effect of illicit drugs and methadone [12]), the incompatibility of HAART uptake with an irregular life style and the psychological effects of HAART ranging from not understanding medical jargon to the confrontation with ones condition and dealing with a perceived negative attitude towards oneself from medical care takers [12]. In summary, less access to HAART, later initiation and lower therapy adherence play an important role in the less spectacular declines of AIDS and death observed in the HAART era among HIV-infected IDU than among other risk groups [20,33-35].

Infections typical among HIV-infected IDU

Owing to their life style, injecting drug users are at higher risk of illness and death than the general population. Some major causes of the excess death rate among IDU are suicide, accidents, overdose, and infectious diseases [36-38]. Unsterile injecting practices (sharing needles, filters or other injecting equipment), drug impurities and poor hygiene and living conditions contribute to the elevated risk for numerous serious infections which include skin infections, endocarditis, pneumonia and tuberculosis [7,39]. Unsafe injection practices are the reason why the transmission rates of blood borne viruses such as hepatitis B and C are also high in this population [40]. Since HIV was introduced into this group the prevalence of tuberculosis also increased in HIV-infected IDU due to the increased susceptibility for tuberculosis caused by HIV [41].

Tuberculosis and HIV

Tuberculosis is a disease caused by Mycobacterium Tuberculosis and is predominantly spread by droplet infection via coughing. Infection usually involves the lungs and normally the primary infection heals, but can leave some surviving tubercle bacilli: the mycobacteria are phagocytosed by macrophages in the lung but M. Tuberculosis can prevent intracellular fusion with liposomes which carry the enzymes which would break it down. With lowering of the host resistance, even after many years, reactivation of the infection can occur. The lifetime risk of progressing to active disease among latently infected persons is approximately 10% [42] but the risk is 5-10% per year in individuals with HIV infection [43]. Pulmonary tuberculosis is the most common form of the disease but tuberculosis can also affect other organs such as the gastrointestinal tract, genito-urinary system and the central nervous system (extra pulmonary tuberculosis). It seems that infection with M. tuberculosis does not protect against future re-infection [44,45]. Patients with pulmonary tuberculosis are administered 6 months of isoniazid and rifampin, sometimes longer in HIV-infected individuals and individuals with extra pulmonary tuberculosis [46]. Due to drug interactions a non-rifampin based regimen is necessary when treating tuberculosis in individuals on HAART.

HIV-infected individuals are particularly susceptible to tuberculosis, both through newly acquired infection and reactivation of dormant bacilli [47-50], and the incidence is especially high among HIV-positive patients in Sub Saharan Africa, where many individuals die prematurely of
tuberculosis [51]. In Europe the incidence is elevated in Eastern Europe [52]. In Western Europe, tuberculosis is more common among HIV-infected drug users than among other HIV risk groups and the risk of tuberculosis increases from North to South [53,54]. Compared to the general population the incidence of tuberculosis is elevated in HIV-negative IDU and even higher in HIV-positive IDU [41]. A problem in screening HIV-infected individuals with tuberculin skin testing is the decreased reactivity to such testing (anergy) with advancing HIV infection [55]. Although M. tuberculosis bacilli thrive in immunosuppressed individuals, a notable feature of pulmonary tuberculosis in HIV Infection compared to other opportunistic infections is that it presents at widely differing CD4+ T cell counts, although the risk does increase with the degree of immunosuppression [56,57]. In contrast, extra pulmonary tuberculosis is associated with more profound immunodeficiency [58]. Initially pulmonary tuberculosis was not classified as an AIDS defining disease but it was added to the AIDS case definition in 1993 (defined by the centers for disease control) [8,9]. In developed countries tuberculosis is not clearly associated with HIV disease progression [59-61] and the advent of HAART has greatly reduced the risk developing tuberculosis [62].

Hepatitis C virus and HIV

Hepatitis C virus (HCV) is a virus which actively replicates in the liver and can cause serious liver disease within 2-3 decades after infection [63]. Failure to clear the virus occurs in 55-85% of infected individuals after which the virus can persist in a patient for years in the absence of symptoms. At least one fifth of these chronically infected adults develops liver cirrhosis within 20 years which eventually can progress to potentially lethal liver failure or hepatocellular carcinoma [64]. HCV is mainly transmitted through blood-blood contact and infection with HCV, even when an antibody response is present, does not protect against new infection in the future [65]. Some countries, such as Egypt, have very high prevalence rates in the general population [66]. In general however, approximately 1% of the general population in Western Europe is infected. The highest HCV prevalence rates are seen in individuals with repeated direct percutaneous or blood exposure such as hemophilia patients and injecting drug users, with prevalence rates of 60-90% [67]. Nowadays in Western Europe, with screening of blood products, the largest risk group for HCV transmission is IDU [68]. It is estimated that at least 1 million up to possibly several million individuals are infected with HCV in the European Union, of which approximately 500 000 are IDU [68]. Risk reduction programs such as needle exchange programs that were targeted to reduce the incidence of HIV infection among drug users were less effective in reducing the incidence of hepatitis C virus infection [69,70]. One reason for this is that hepatitis C virus is transmitted at least 10 times more efficiently through blood contact than HIV [71,72]. Another reason why the risk of infection with HCV is much greater than with HIV is the higher prevalence of HCV among IDU than of HIV.

Hepatitis C virus is a single stranded RNA virus of approximately 9400 nucleotides classified into the hepacivirus genus of the family of flaviviridae, and it is estimated to be 500-2000 years old. Like HIV it has a sloppy replication system (lacking proof-reading activity) leading to high sequence variability. To date there are 6 different genotypes which are further classified into subtypes. Variability varies across the genome with a mean similarity between genotypes of 65-70%. Isolates of the same subtype differ by 5-10%. Due to random mutation the strains within a host also show a sequence variability of 1-2% (so-called quasispecies). The distribution of HCV subtypes varies by geographic region. In Europe and the USA the predominant subtypes are 1a, 1b, 2a, 2b and 3a. Among IDU subtypes 1a and 3a are the most prevalent subtypes. Genotype 4,
originating from the Middle East and Africa is now also found in IDU across Europe [73,74]. The genome variability of HCV allows for studying transmission patterns which was done in chapter 5.

**Drug use and the immune system**

In the absence of treatment, infection with HIV is characterised by gradual erosion of the immune system, the number of CD4+ T cells in peripheral blood gradually decreases, which leads to the susceptibility to a wide range of (opportunistic) infections and ultimately death. Even in the absence of HIV infection the immune systems of drug users have been reported to show abnormalities. Whether and how drugs affect the immune system (suppression or activation) may depend on the type and frequency of drug use, although reports have been inconsistent [75,76]. Opiates have been shown to suppress the function of T-lymphocytes but not in all studies [77]. T-cell reactivity has been seen to be significantly depressed in IDU with very high injecting frequency of more than 50 times per month [78]. It is unlikely that defects or abnormalities in the immune system are purely the result of drug use. A combination of different factors probably plays a role besides the immune modulating effects of drugs [77] such as exposure to injected impurities and microbes, and differences in lifestyle [38,38,79]. Despite the specific characteristics of drug users, the average time from HIV seroconversion to AIDS and death did not seem to differ from that in other risk groups in the time when highly active antiretroviral therapy was not yet widely available [14]. However, within specific risk groups, differences in immune status may still play a role in HIV disease progression [80].

**The European Seroconverter Study among IDU**

The European Seroconverter Study was initiated in 1994 to address questions on the natural history of HIV infection in IDU. Eight prospective cohorts in 6 European countries participate in the collaboration which was initiated by the Municipal Health Service in Amsterdam (figure 1). The multi-centre co-operation was necessary to obtain a cohort with sufficient numbers of so-called HIV seroconverters and disease outcome to be able to adequately address questions on the course of HIV infection. Seroconverters are individuals for whom the dates of the last HIV-negative and first HIV-positive test are available allowing reliable estimation of the date of HIV infection so that bias by the unknown duration of infection is not present when studying progression of HIV infection [81]. HIV-infected IDU seroconverters who had injected drugs between 1979 and prior to their HIV infection were included in the study. Every 3-6 months cohort participants underwent standardised clinical examination, blood testing and completion of questionnaires at each separate cohort. Data were sent to the coordinating centre in Amsterdam where a joint database was constructed. Data were collected, cleaned and merged. After 1994 the joint database was updated twice: in 1998 and 2002 (see table 1 for the number of participants by site). For the present thesis we studied the impact of the widespread use of HAART on HIV disease progression (chapters 2 and 3) and the risk of tuberculosis during HIV infection in IDU (chapter 4). For two studies on hepatitis C virus infection (chapters 5 and 6) an additional cohort participated (the Italian Seroconverter Study among IDU). In one study on the impact of the pre-seroconversion immune status on HIV disease progression, only IDU from Amsterdam participated (chapter 7).
Figure 1. Sites participating in the European Seroconverter study among injecting drug users.

Table 1. Number of participants by site in the European Seroconverter Study among IDU

<table>
<thead>
<tr>
<th></th>
<th>Valencian</th>
<th>Edinburgh</th>
<th>Amsterdam</th>
<th>Glasgow</th>
<th>Geneva</th>
<th>Paris</th>
<th>Innsbruck</th>
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<tr>
<td>Total no. of</td>
<td>280</td>
<td>185</td>
<td>123</td>
<td>70</td>
<td>61</td>
<td>40</td>
<td>30</td>
<td>789</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. with AIDS</td>
<td>57</td>
<td>69</td>
<td>33</td>
<td>11</td>
<td>16</td>
<td>11</td>
<td>11</td>
<td>208</td>
</tr>
<tr>
<td>No of Deaths</td>
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<tr>
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<td>26</td>
<td>8</td>
<td>13</td>
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<tr>
<td>Pre AIDS</td>
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<td>36</td>
<td>23</td>
<td>9</td>
<td>5</td>
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