Epidemiological studies among injecting drug users infected with HIV: highly active antiretroviral therapy, tuberculosis, hepatitis C, immunology
van Asten, L. C. H. I.

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Chapter 8

General discussion
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HIV disease progression in the era of widespread HAART

Despite smaller effects than in most other risk groups, injecting drug users (IDU) have clearly benefited from the availability of highly active antiretroviral therapy (HAART). Although receipt of HAART was delayed in IDU, at the population level a reduced risk of AIDS of approximately 30% was already seen in the initial period of HAART availability in 1996-1997 (chapter 2 and 3). For death the risk reduction was somewhat greater, around 37% in this initial HAART period. However it was of a lesser magnitude than the 50%-64% initial improvements recorded in other risk groups [1,2].

With ongoing HAART availability the risk of human immunodeficiency virus (HIV) disease progression to AIDS and death has continued to decrease further. However, in chapter 3 we showed that the initial risk reduction for progression to AIDS was greatly underestimated when pre-AIDS deaths due to natural causes were not accounted for. These are deaths which are not due to overdose, suicide, accidents, or homicide which occur in individuals who have not yet been diagnosed with an AIDS defining disease. In IDU these pre-AIDS death causes are common and are associated with progressing HIV disease [3,4]. For death, risk reductions seemed to be underestimated in the complete HAART era, not only in the initial period of availability, when non-natural deaths, which are not associated with HIV disease progression, [4] were included as HIV-related outcomes as has been done in all previous studies. Excluding these non-natural deaths, the risk of death due to natural causes had decreased by 75% in HIV-infected IDU in the 2000-2001 period which compares to the reported risk reduction of death in HIV-infected hemophilic men but is lower than the 91% reduction in HIV-infected homosexual men [5].

Considering that IDU have less access to treatment and more problems with treatment adherence [6-8] a 75% reduction in the risk of death is not an unsatisfactory result. Greater reductions in risk of death will also be difficult to achieve as long as IDU are not treated for hepatitis C virus (HCV) infection which is almost universal in this group (chapter 5). Liver related mortality has increased among IDU in recent years due to the life lengthening effect of HAART [9,10] and the relatively long incubation period of HCV. Although not all IDU are inadequately adherent, optimal treatment adherence by all IDU will be difficult to achieve. Treatment adherence is also difficult to achieve for groups other than IDU such as younger individuals and depressed persons. An in-depth study among hard drug users in Amsterdam illustrates the multiple barriers which can play a role in this problem [11]:

1) Owing to years of lack of sleep, lack of hygiene and proper nutrition hard drug users often have a poor physical condition which makes it more difficult to cope with side effects. This includes a perceived decreased effect of illicit drugs, sedatives and methadone. 2) An irregular lifestyle is incompatible with strict HAART regimens especially when large pills or liquid medication are involved. Being occupied with drug use all day also has a negative effect on HAART compliance. Shelter, peace and quiet, and privacy are also necessary for adherence but not available to all drug users. A lack of financial means may also be a barrier for adherence when individuals are required to stick to a prescribed diet for specific drugs or when they are required to contribute to the payment of HAART. 3) Psychological effects due to HAART exist. HAART can confront HIV-infected IDU with their condition which can lead to individuals who ‘tend’ to forget their medication. Furthermore, HIV-positive drug users often have a hard time, and feelings of depression negatively affect adherence. Also medical jargon results in insufficient and incorrect knowledge of HAART among IDU, and a lack of social support and the perception that doctors have a negative attitude towards them is demotivating for adhering to treatment.
The development of easier regimens and directly observed therapy in which HAART is provided in combination with methadone provision will probably make HAART uptake and adherence easier for larger proportions of IDU although the circumstances of some IDU may never be compatible with any type of regimen.

**Tuberculosis in IDU**

HIV-infected IDU are highly susceptible to tuberculosis disease caused both by reactivation of latent disease and by recently acquired infection [12-15]. In chapter 4 we showed that among IDU, the risk of tuberculosis varies with the duration of HIV infection: it is elevated relatively early in infection (years 4-6) and even more so in late HIV infection (after year 9), independently of CD4+ T cell count. Although we were unable to ascertain this directly as the study population did not include HIV-negative IDU to compare with, the risk of tuberculosis was probably already increased in the initial years of HIV infection: the incidence rates in the first 3 years of HIV infection were higher than reported rates for HIV-negative IDU (up to 18.8 per 1000 person years vs. reported rates between 0 and 3.0 per 1000 person years in HIV-negative IDU [16-19]. A recent study among HIV-infected South African miners [20] showed tuberculosis risk to double within the first year of HIV infection with only slight increases thereafter. This trend with ongoing HIV infection may differ from the trend that we found among European IDU due to differences in setting, background prevalence of Mycobacterium Tuberculosis, and perhaps disease pathogenesis. As HIV-positive persons are known to be susceptible to both reactivation of latent M. Tuberculosis infection and to new infections of M. Tuberculosis [18-22] we hypothesized that in IDU the variation we found in the risk of tuberculosis during HIV infection might be explained by varying degrees of reactivation and re-infection with duration of HIV infection: possibly, reactivation of latent M. Tuberculosis infection occurs earlier in HIV infection, perhaps followed by a relatively silent period and later in HIV-infection, (after 9 years in our data), susceptibility to new tuberculosis infection is increased. The relative contribution of both mechanisms to tuberculosis disease in HIV-positive IDU can be studied by using DNA fingerprinting of M. Tuberculosis or genotyping, with clustering of cases indicating new infections. To date, no such studies have investigated whether tuberculosis cases earlier in HIV infection show less clustering than tuberculosis cases later in HIV disease. Even if duration of HIV infection is not known, determining the relative contribution of reactivation of latent infection and new infection is relevant in planning intervention strategies. This is especially relevant among HIV-positive IDU in Amsterdam as it remains to be elucidated why the incidence of tuberculosis is so much higher there than in other Central and Northern European cities (chapter 4). The higher incidence is striking because in the general population the incidence of tuberculosis is relatively low in central and Northern European countries including the Netherlands [21]. If the elevated risk in Amsterdam is due to reactivation of latent tuberculosis infection it can be decreased by the provision of prophylaxis as is done in several cities in Europe (chapter 4). Prophylaxis has been shown to diminish tuberculosis incidence in latently infected by 50% and more in the short term [22-25]. However, it may be difficult to target the total IDU risk group and ensure sufficient treatment adherence. Reactivation of latent disease is thought to be less likely in the developed world where tuberculosis prevalence is low, however IDU are an exception in that they have a higher rate of previous infection with tuberculosis than the general population [26]. Also newly acquired infections are likely to play a major role in tuberculosis disease burden in IDU as shelters for homeless individuals are known foci of tuberculosis transmission [27-30]. Comparing M. Tuberculosis strains of IDU with those of non-IDU may help in estimating whether and at which intensity tuberculosis is transmitted from IDU to the general population. This may differ among
European cities, depending perhaps on issues such as the availability of shelters and the extent to which IDU receive social support and still live at home as is more the case in the Valencian region of Spain. Another molecular epidemiological issue to investigate among HIV-infected IDU is whether recurrence of tuberculosis within the same individual is due to exogenous re-infection or due to relapse of previous infection, the latter implicating that treatment administration needs to be better tailored to this group to improve adherence and treatment success. However if mainly similar or even identical strains circulate among IDU, molecular techniques may be of limited help in discriminating between relapse and new infection. Furthermore future studies with follow-up later in the HAART era or information on individual HAART use are needed to understand how much the risk of tuberculosis among HIV-infected IDU has decreased in the HAART era.

Hepatitis C virus infection in IDU

**Effect of HCV on HIV disease progression**

It is well established that HIV causes faster progression of hepatitis C virus (HCV) infection to liver cirrhosis [31-33]. Alternatively, whether HIV disease progression is enhanced by HCV is under debate with findings from different studies being inconsistent [34-42]. The focus may have to shift to studying the effect of specific HCV genotypes instead of simply studying the presence of HCV infection regardless of genotype. In hemophilic men HCV genotype 1 (not further distinguished by subtype) was previously associated with more rapid progression to AIDS, but not in IDU [43,44]. In chapter 6 we confirmed the finding that subtype 1 is not associated with enhanced progression to AIDS in IDU although it may be associated with enhanced progression to low CD4+ T cell counts. In our study, HIV disease progression was especially enhanced in those harboring HCV infection involving more than one HCV genotype. This association needs confirmation by further studies as it has not been studied previously and is based on small numbers. The effect of mixed HCV genotype infection is particularly relevant for IDU, as IDU may remain exposed to HCV by risky injecting behaviour which potentially causes infection with mixed HCV genotypes. However, individuals who are repeatedly exposed to HCV may not necessarily carry multiple genotypes. IDU have been shown to switch from one genotype to another over time or switch from one genotype to multiple genotypes and vice versa, or might in due course clear HCV RNA altogether [45-47]. Also super infection with divergent strains of the same genotype is not uncommon, but will not be detected when the subtype is determined but not the extent of virus variability [46,48]. In individuals who switch from one genotype to another it is not known whether the previously present genotype actually is cleared or whether it remains present at undetectable levels. Also which viral and host factors predict spontaneous clearance of HCV needs to be further ascertained. Due to the risk of re-infection (through continued use of previously used injecting equipment) in IDU and possible clearance of the virus, HCV genotype should ideally be measured prior to HIV infection and longitudinally at yearly intervals within HIV-infected individuals to gain a better understanding of the effect of HCV genotype on HIV progression. Furthermore as studies on the effect of HCV genotype on HIV disease progression to date are few and small, larger studies are necessary to confirm current findings, especially among HIV-positive IDU among whom hepatitis C virus (HCV) infection is almost universal (chapter 5). Whether the risk of HIV disease progression among IDU with chronic HCV infection of different genotypes differs from IDU without HCV infection will be difficult to ascertain as numbers of the latter group are often too few to comprise a large enough comparison group. This problem underlies the bias present in the many studies that have already studied the relationship between HCV genotype and HIV progression regardless of HCV genotype. They are all seriously limited by an extremely disproportionate distribution of risk groups across the HCV-positive and HCV-
negative individuals that were being compared [34-42]. All the studies reporting that HCV accelerates HIV disease progression [36,39-42] as well as some of the studies reporting no effect of HCV [34,37] included an HCV-positive group comprising almost exclusively IDU (ranging from 75% to 92%), and included almost no IDU in the HCV-negative group (ranging from 5% to 14%). As IDU are known to exhibit faster progression in the HAART era due to the lower proportion of person time spent on HAART, comparing such different risk groups can potentially cause serious bias. Some studies finding no effect of HCV infection feature somewhat less extreme disproportionality in the risk group distribution across HCV exposure groups: in a study in Taiwan 17% of HCV-positive and 0.8% of HCV-negative individuals were IDU [35] and in a study among pregnant women in the USA, in which the risk group distribution is not clearly stated, 72% of HCV+ women and 30% of HCV- women reported hard drug usage during their pregnancy [34]. Besides not adjusting for the possibly varying effect by HCV genotype, another limitation of all but one of all the studies on this issue [36] is that they were conducted in prevalent cohorts, therefore lacking defined dates of HIV acquisition[34]. Thus whether HCV affects the course of HIV infection remains controversial. Although sufficient numbers will be difficult to attain, studies with homogeneous risk group distributions or within single risk groups, in which HCV genotype is also accounted for, are necessary to shed further light on this issue.

Impact of HCV on death in IDU and treatment of HCV
Since the life expectancy of HIV-infected IDU has increased due to HAART, the impact of HCV infection in this group has become more evident: the risk of AIDS-related death has been greatly reduced and individuals live long enough for liver disease to develop as illustrated by the significant increase in the proportion of liver related deaths among IDU in the past years [9,10]. IDU, whether HIV-infected or not, often do not receive treatment for HCV and treatment guidelines in the recent past even discouraged their treatment [49,50]. However, to limit liver morbidity and mortality and for the prevention of further spread of HCV it is important that IDU are treated. Important advances in the treatment of HCV have occurred and several recent guidelines now recommend treatment of IDU [51-53]. However barriers for HCV treatment are multiple. Most importantly, the psychological side effects such as depression and emotional lability known to be caused by interferon treatment [54] may be more pronounced in IDU, a fragile population with pre-existing problems and lack of social support. This not only causes treatment discontinuation, a large proportion of IDU even refuse to initiate treatment for fear of its side effects [55]. Adherence to HCV therapy is further jeopardised by several other social and psychological factors, many the same as which affect adherence to HAART. In general, in adherent individuals, HCV treatment success is not achieved by everyone. Sustained response rates vary between 40-80% for the newest treatment combinations (pegylated interferon and ribavirin) depending on the HCV genotype and in the absence of HIV [9,56]. Genotype 1, which is relatively common among IDU, and genotype 4, which has entered the European IDU population (chapter 5) [57], have lower treatment success rates than genotypes 2 and 3 [56]. We found that 14% of HIV-infected drug users in Western Europe were infected with these types (chapter 5). Finally, an important consideration among physicians who are reluctant to treat HCV infection in IDU is the risk of HCV re-infection after successful treatment, when unsafe injecting is continued, which can be as high as 50% [58]. Needle exchange programs effectively diminish needle sharing and prevention measures should include the risk of sharing other equipment which also readily transmits HCV, such as cookers, spoons and filters [59,60]. It may be possible to keep re-infection rates low among IDU as illustrated by a low re-infection rate of 7% over an average follow-up period of 2,5 years in a study among French IDU [61]. Since low re-infection rates are not
sufficient to halt HCV transmission, treatment of IDU can play a role in reducing HCV transmission in this group.

For HIV-HCV co-infected individuals it is advised that HCV is treated prior to initiating HAART due to the toxic effects of all drugs. Treatment success is higher when HCV is treated in the stage of acute infection before it has evolved to chronic infection [62]. It is however difficult to recognize acute infection as disease onset is frequently asymptomatic. However to limit HCV transmission and to improve treatment success it might be best to treat HCV-infected IDU during acute infection, arguing for repeated testing for HCV in IDU seen in treatment centres. It also remains to be determined whether a fast initiation of treatment, due to the time pressure involved in treating acute infection, is achievable in IDU without compromising the level of preparation they need. Treatment of HCV is more successful in IDU when combined with methadone maintenance therapy and with close supervision of physicians [63]. Individualised management and a multidisciplinary approach are advised in the management of HCV infection in IDU, perhaps with an integration of HCV treatment within substance abuse treatment [55]. Many current studies on the treatment success of HCV are performed in non-drug users but should be complemented by studies focusing on drug users as they comprise the largest risk group of HCV infection [64]. Optimal treatment strategies in those with HIV-HCV co-infection also need to be determined. Considering that great reductions in AIDS-related morbidity and mortality have been achieved among IDU due to HAART, which consists of complicated treatment regimens and is administered for years, treatment of HCV, which is a matter of months, should be feasible among IDU when properly tailored. As noted by Edlin et al: ‘If poor adherence were a contra-indication to therapy, most medical conditions would go untreated. Nor are patients whose behavior could cause a recurrence of a condition generally denied treatment in other settings’. Some examples of such other patients are smokers, individuals with alcoholic liver disease and persons with sexually transmitted infections who engage in high-risk sexual practices [60].

HCV in young drug users and the spread of HCV
Young drug users should be of special focus for prevention particularly because HCV is highly infectious. Young drug users to whom injecting is new may not have their own injecting equipment and be inclined to share and they may need help with injecting [65]. Requiring help with injecting is a demonstrated risk factor for acquiring HIV which is less infectious than HCV [66]. As mixing with experienced injectors occurs, initial injecting episodes may be particularly risky when unsafe injecting practices are involved, even when syringes and needles are not directly shared but e.g. cookers, spoons, and filters are [59,67]. Although patterns of drug use change with time [68] and the prevalence of injecting has decreased in recent years, [69-71], minimal exposure to HCV can result in infection [57]. In the Amsterdam Cohort Study the HCV antibody prevalence was 91% among young (age <30 years) drug users in the 1980’s, and 44% in the 2000-2004 time period [69]. Although younger individuals more often clear the virus, further research is necessary to determine the risk of chronic hepatitis C infection and its pathogenesis in young individuals: e.g. to determine whether young individuals who have apparently cleared the virus are perhaps viremic at currently undetectable levels and what the clinical consequences might be in the long term. In chapter 5 we have shown that the HCV epidemic within each European city is diverse, as multiple strains of various subtypes circulate within each country. Transmission of HCV between IDU populations from different European cities has occurred on a very large scale, since strains from all the different European cities are highly dispersed throughout the phylogenetic tree of this study population. In future efforts to prevent HCV infection among IDU in one country, the high degree of virus exchange between IDU across European borders should be considered: injecting
practices applied when IDU travel abroad or when they contact visiting IDU in their own country may have to be addressed. For prevention purposes it can also be useful to understand whether younger IDU mix with older IDU or whether segregated epidemics occur within different age groups: do younger drug users infect each other or is there a substantial spillover from older generations? So far this has only been studied in Amsterdam and the data from young drug users shows mainly diversification of old strains and the introduction of new HCV strains over time. Low genetic variability between strains from 2 different time periods were also incidentally observed indicating that mixing among generations perhaps does occur [69].

**Immunology**

The mechanism of the CD4+ T cell depletion during HIV infection is still not entirely clear. Direct killing of infected cells by HIV seems to play a relatively minor role [72]. HIV causes the immune system to be in a continuously activated state: T cells are activated, including non-HIV specific T cells, and therefore go through rapid cycles of cell division after which most of the cells which are generated by cell proliferation will normally die [73-75]. The rate of CD4+ T cell turnover in HIV infection is lower than was previously postulated [76,77]. Loss of CD4+ T cells, driven by immune activation, at a rate higher than new T cells are normally produced by the immune system, probably causes small net losses of CD4+ T cells which leads to the gradual decline of CD4+ T cell numbers in HIV-infected individuals [74]. Whether the capability to produce new CD4+ T cells by the thymus is also impaired in HIV-infected individuals is under debate.

In chapter 7 we showed that in IDU the immune status already prior to HIV infection affects the disease course after HIV seroconversion. We measured pre-seroconversion CD4 T-cell receptor excision circle (TREC) content assuming that higher CD4 TREC contents reflect a lower rate of infections experienced throughout life and perhaps a genetic predisposition to respond with lower levels of immune stimulation when going through an infection. IDU with high TREC contents prior to HIV infection lost their CD4+ T cells at a significantly slower rate during HIV infection than IDU with lower pre-seroconversion CD4 TREC contents indicating that a better immune status prior to infection is associated with slower disease progression. Studies on the effect of the pre-seroconversion immune status are very limited with only one other study among homosexual men in which lower levels of pre-seroconversion immune activation (CD70 expression) also were associated with slower HIV disease progression to AIDS [78]. However CD70 expression merely reflects an individual's immune status at a specific moment in time whilst the average CD4 TREC content is a more cumulative and therefore better marker of an individual's immune status history [79]. Previously, experiencing infections during HIV infection has also been associated with lower CD4+ T cell numbers, although only in the first 5 years of HIV infection [80]. In contrast to this association with self-reported infections, the difference between IDU with low and high TREC content was more clear-cut with individuals with the highest TREC content displaying higher CD4+ T cell trajectories of other IDU as did in the analysis of self-reported infections after 5 years. Self-report is likely to be less reliable than laboratory assessment of markers and besides, TREC content mirrors one's immune status history where self report during HIV infection conveys no information on infections experienced in the past prior to HIV infection. We also studied the predictive value of the total number of TREC's which is reflective of thymic function. IDU with higher pre-seroconversion total TREC numbers tended to display a slower rate of CD4+ T cell loss during HIV infection, which was borderline significant (p=0.06). Due to small numbers our study may have been underpowered and therefore remained inconclusive. To confirm the importance of
both pre-seroconversion immune status and pre-seroconversion thymic function not only further research is required among IDU but also among other risk groups.

In the same study (chapter 7), higher injecting frequency was associated with slower CD4+ T cell decline. As injecting frequency was not correlated with CD4+ TREC content, the injecting frequency, even when measured longitudinally, is assumably not associated with the intensity of infections experienced throughout life because injecting frequency conveys little information on lifestyle, and on the infections and drug impurities encountered. But current injecting frequency itself might affect the immune system of IDU as was also previously demonstrated by a decreased T cell proliferative response in HIV-positive frequent injectors in the Amsterdam cohort [81]. Furthermore another factor, the frequent borrowing of injection equipment, has previously been shown to be associated with higher CD4+ T cell counts already prior to HIV infection [80] and slower progression of HIV infection to low CD4+ T cell counts [80]. However in general, research regarding the immune system in HIV infection is not often performed among IDU and certainly confirmation of the results is lacking. Another aspect to keep in mind is that when studying seroprevalent HIV-infected IDU, IDU with less severe immune deficiency or slower disease progression may simply display different injecting behaviour than IDU with advanced immunosuppression or serious clinical symptoms, thus causing spurious associations in studies of IDU. Results from a controlled trial in monkeys suggest that AIDS progression is retarded by opiate dependency [82]. This might be explained through the following mechanism: as activation of T cells leads to production of human immunodeficiency viruses, then suppression of the immune system through opiates [82-84] might reduce viral load production and slow AIDS progression [82]. However, contrary to this finding, some laboratory studies have shown that cocaine and heroin promote the growth of HIV in vitro. In contrast to in vitro and animal studies, the majority of epidemiological studies fail to find an effect of drug use on HIV disease progression [85-88]. According to Donahoe, studying IDU as a group causes the discordance between laboratory studies on the one hand and epidemiological studies on the other [82] and he poses several reasons which may explain why epidemiological studies fail to find any effect of drug use: Importantly different drugs, which are regularly used in combination, have different effects on the immune system (suppression versus activation) and even individual drugs, when used alone, are associated with varied immunomodulatory capacities [82,83,89]. Thus opposing effects may counter each other, both within individual IDU exhibiting poly-drug use as well as among different IDU using different drugs resulting in a net zero effect of drug use on HIV infection in epidemiological studies. This problem is further exacerbated by the fact that IDU largely differ in their dose regimens and even individual drug users may not use consistent drug dosages through time or even from one day to another. Donahoe also suggests that selection bias may impact on the results of epidemiological studies in the sense that IDU who are in poor health as well as those who are in relatively good health with relatively stable dependencies may be less likely or unable to participate in studies. Finally, most epidemiological studies focus on all AIDS defining diagnoses whilst there are indications that progression more specifically to neurological AIDS defining events might be enhanced in IDU [90,91]. Moreover, all epidemiological studies have data on self-reported drug use, which might be subject to recall bias and socially desirable answers.

Further immunological research may help to understand the still unresolved issue of whether drug use retards, accelerates or has no effect on progression of HIV infection [82,88,90,92], especially when the different characteristics of IDU (such as drug use frequency, dosage, type of drug(s) used, and perhaps lifestyle) are kept in mind instead of grouping IDU together and assuming this...
group to represent a homogenous entity. One previous epidemiological study shows that use of mainly heroin is associated with a sharper CD4+ T cell decline but this effect disappeared 6 months after HIV seroconversion. If in fact the effects of drugs are short lived then this might explain the discrepancy between laboratory and epidemiological studies (which are generally conducted over longer time periods than laboratory studies) [80]. A better understanding of the immunology of HIV infection in IDU is not only relevant for HIV-infected drug users but research among IDU might also give rise to clues which can lead to a further understanding of HIV pathogenesis in all risk groups.

Because the prevalence of co-infections is high in HIV-infected IDU, further study of the immunological and virological consequences of such co-infections might help in discovering additional factors that affect HIV disease progression and the health status and well being of IDU. Better understanding of the immunological implications of HCV-HIV co-infection might help in clarifying the issue of whether HCV infection does or does not influence HIV disease progression and the significance of HCV genotype in both HIV disease progression and HCV disease progression. CD4+ T cells and CD8+ T cells are involved in the control of HCV infection but as HIV infection is characterized by the loss in numbers and function of CD4+ T cells the effect on the immune system of dual HCV/HIV infection remains to be further explored. Interestingly HCV is not directly cytopathic and liver lesions are mainly related to immune-mediated mechanisms, which are characterized by a predominant type1 helper cell response. Also co-factors influencing the outcome of HCV infection including age, gender and alcohol consumption are poorly understood and might be studied from an immunological perspective. Also the interaction between M. Tuberculosis and HIV remains to be further explored. HIV and M. Tuberculosis both target the immune system (macrophages), and together with HCV, these 3 pathogens evade host defense systems leading to persistent infection.

**In conclusion**

Many aspects of HIV infection in IDU but also in non-injecting drug users remain to be further explored: how to improve adherence to HAART, the optimal treatment strategy of HCV, the long term effects of HCV infection, methods for decreasing the prevalence of tuberculosis, the immunological aspects of drug use in HIV infection, and the interactions between co-infections such as HCV, tuberculosis, and HIV. Many of the issues regarding HCV and tuberculosis also need to be further explored in HIV-negative drug users such as the long term consequences of HCV infection and the best treatment strategies, and whether the prevalence of tuberculosis in Amsterdam which is very high among HIV-positive IDU is also high in HIV-negative IDU. Although trends in drug use change over time, research among injecting drug users remains relevant. The prevalence of injecting has greatly decreased in the recent past [69-71], but as injecting prevalence seems to increase and decrease in cycles [68] the popularity of injecting drugs may rise again, as demonstrated by a recent study in London [93]. At present IDU form a large group of people living with HIV in Europe and Asia, and new HIV epidemics in this risk group still occur as illustrated by the recent epidemics in Portugal and Eastern Europe [94].


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