Slow progression of hepatic fibrosis in chronic hepatitis C virus positive, HIV negative intravenous drug users during the first two decades of infection

The high prevalence of hepatitis viruses C (HCV) and B (HBV) as well as co-infection with human immune deficiency virus (HIV) among intravenous drug users (IDUs) is by now common knowledge [1,2]. Co-infection with HCV and HIV is reported to be associated with lower rates of spontaneous HCV clearance, faster progression of chronic liver disease to cirrhosis and lower response rates to anti-HCV treatment [3,4]. Thus most, although not all studies report an accelerated course of hepatic fibrosis in HIV/HCV co-infected patients [5–7]. In contrast to HCV-HIV co-infection, the natural history of chronic HCV infection in the relatively large population of HCV mono-infected (HIV negative) IDU population receives much less attention. A literature search revealed conflicting data regarding the long-term natural history of chronic hepatitis C and progression of fibrosis in HIV negative IDUs [5–7]. In this context it should be mentioned that additional risk factors except for HIV, i.e., overdose of opiates, excessive alcohol intake, malnutrition and others may have an impact on the natural history and survival of HCV infected IDUs. Up to date epidemiologic data on prevalence and natural history of hepatitis viruses in IDUs are mainly deducted from estimates and not from accurate public health, molecular epidemiologic or clinical surveillance data [8–11]. A recent systematic review published in the Lancet summarized HCV prevalence data in IDUs from 77 countries [9]. According to this analysis (which the authors acknowledge as an under-estimate) there are approximately 10 million anti-HCV positive IDUs worldwide, the majority living in China (~1.6 million), in the USA (~1.5 million), and Russia (~1.3 million). Anti-HCV prevalence among IDUs ranged between 60–80% in 25 countries and above 80% in 12 countries. A similar survey on the global epidemiology of HIV among IDUs was reported in 2008 by the same group [8]. Prevalence estimates from 61 countries containing 77% of the world’s total population, aged 15–64 years, suggest that there are at least 15.9 million IDUs worldwide, mainly in China, the USA, and Russia. The mid estimates of HIV prevalence in IDUs in these countries are 12%, 16%, and 37% respectively. The authors estimate that about 3 million IDUs worldwide are HIV positive [8]. Based on these two large surveys, and irrespective whether these are under-estimates, it is clear that the global burden of HCV carriers among IDUs far exceeds the numbers of HIV carriers. Furthermore, IDUs frequently acquire HCV before HIV infection [12,13]. Consequently, there is an interest in assessment of the natural history of HCV infection and the risk of progressing fibrosis in HIV negative IDUs.

In the present issue of the journal, Dr. Kielland and co-workers from Norway evaluated the risk of developing hepatic fibrosis over a long follow-up of up to 35 years in injecting IDUs infected with HCV, presumably being HIV negative [14]. This report is in fact an extension of a recent publication by the same authors entitled “All-cause and liver-related mortality in hepatitis C infected drug users followed for 33 years: A controlled study” [15]. The study population consisted originally of 523 anti-HCV positive IDUs admitted for treatment over a period of 15 years (1970–1984) to the National Clinic for Drug Abuse in Norway. The study cohort was officially established in 1991 and consequently, some of the data (i.e., causes of death) were collected retrospectively and others prospectively. At time of analysis in 2008, 220/523 patients died. Liver biopsies obtained at autopsy and serum for HCV-RNA testing were available for analysis for approximately one fifth of the original cohort, namely in 102/220 patients. For most of the patients, age of HCV acquisition was deducted from time of first IV injection. Three sections of each tissue sample were evaluated by two independent pathologists and the Metavir score was used for determination of the stage of fibrosis while the degree of inflammation and autolysis was assessed by a four point scale. Of the study cohort of 102 patients, the mean age at autopsy was 37.3 years; 75% were males, of whom 60% were HCV-RNA positive as determined by an in-house PCR assay (lower detection limit ~100 IU/ml). The mean observation time from HCV exposure to death was 16.9 years.

One important observation of this study suggest that death from liver disease in IDUs in Norway, presumably being HIV negative, is a relatively rare event observed in only 4.9% of HCV-RNA positive patients during the study period, as compared to 0% in HCV-RNA negative subjects. Furthermore, F3/F4 fibrosis was observed in only 16% of HCV-RNA positive chronic HCV patients.
and compared to 2% in those who apparently cleared HCV and were HCV-RNA negative. The 16% rate of advanced fibrosis and only 8% of cirrhosis observed in the study population of 102 autopsied patients is relatively low compared to early reports on the natural history of chronic HCV infection. It is however similar to the figure quoted by Thein et al. who conducted a meta-analysis of 111 studies on the natural history of HCV infection in 33,121 HCV patients and modelled the risk of transition to cirrhosis [16]. In this meta-analysis, stage-specific transition probabilities (which are non-linear) were: F0 to F1 0.117; F1 to F2 0.085; F2 to F3 0.120; and F3 to F4 0.116. As also observed previously in non-IDU patients infected with HCV, extent of fibrosis was proportional to duration of exposure to HCV (and presumably to viremia), being lower than F3 in subjects with chronic hepatitis C who died up to 15 years after HCV exposure. In contrast, F3/F4 fibrosis was identified in 35% of HCV-RNA positive patients who died >25 years post exposure. Most importantly, the availability of relatively large liver tissue samples obtained at autopsy contributed indeed to the accuracy of scoring the degree of fibrosis and avoiding sampling error, which may occur using conventional needle liver biopsies. Cumulative survival of HCV-RNA negative patients was indeed better as compared to the viremic cohort. However, the majority of patients in the cohort who underwent an autopsy died from drug related causes such as opiate intoxication, suicide and accidents, and not from liver disease [15]. Thus almost two thirds of viremic subjects who were autopsied more than 20 years after HCV exposure had practically no or minimal hepatic fibrosis. The results of this study should have been reassuring and may possibly have an impact on the timing and priority of when and if to treat chronic HCV infection in HIV negative subjects in this very difficult population, which is often non-compliant. Thus, delaying therapeutic intervention would enable a chance for longer rehabilitation and future access to the more potent anti-viral agents, which are now in the pipeline. However, the study has a number of technical and methodological limitations, which require further evaluation and confirmation before drawing definite conclusions. These include among others, the relatively small number of IDUs out of the total who underwent histologic evaluation, the limited sensitivity of the HCV-RNA assay used, and the lack of genotyping, which may have an impact on response to treatment and prognosis. Furthermore, the anti-HCV positive/HCV RNA negative control group is presumed to have cleared HCV infection. This may indeed have been the case but confirmation using a radio – immuno blotting assay (RIBA) would have strengthened this assumption. It is indeed unfortunate that the investigators were unable to test the sera for HIV infection. There was only one case of HIV infection in the study cohort, which was not screened systematically for HIV. The authors hypothesize that HIV infection rates are relatively low in Scandinavia and provide a European reference [8] to support this statement quoting a 3.2% prevalence of HIV in 2006 among IDUs in Norway. However, in the absence of HIV testing in the described cohort of IDUs in general and especially in those with advanced hepatic fibrosis in particular, this assessment remains at best an assumption and consequently casts some doubt on the robustness of the conclusions regarding the natural history of HCV infection in this HCV negative IDUs cohort. Yet, regardless of these limitations and provided that these patients were indeed HIV negative, the study results may be representative for large groups of HCV+/HIV– IDU patients who are future candidates for anti-viral therapy during the first two decades of HCV infection with a favourable prognosis concerning their liver disease.

Conflict of interest
The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References