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HCV and Drug Use – What Can Be Learned from the Failure to Control This Epidemic?

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1. Introduction

Around 10 million intravenous drug addicts (IDUs) have been infected by the virus of hepatitis C (HCV) and around 1.2 million are HBsAg positive. Clear geographical differences exist in prevalence ranging in Western Europe between 37 and 98 % (1). At WHO's 63rd World Health Assembly in May, 2010, a resolution was passed to establish "goals and strategies for disease control, increasing education and promoting screening and treatment of people infected with HBV and HCV". In 2011, the WHO argued that injecting drug users (IDUs) are a key group that needs to be specifically targeted for prevention and treatment of viral hepatitis. At a time when a worldwide significant reduction in the HIV epidemic among drug users (DU) is observed, the spread of HCV infections is not controlled. If large variations are observed between countries and regions, prevalence of HCV infection of more than 70 % has been reported among recent-onset DUs (2) and, in 2009, in a city, Vancouver, with one of the most diversified and publicized panel of care services for substance users, Grebely et al. could make the statement that "overall, the rate of new HCV seroconversions in this cohort in the study period was about 25 times the rate of HCV treatment uptake. There are extremely low rates of HCV treatment initiation and very limited effectiveness, despite a high prevalence of HCV infection in this large community-based cohort of inner city residents with access to universal healthcare". It underlines the limits of the risk reduction policy which has been advocated and promoted for the last 20 years (3).

This quasi universal observation may be explained by differences between the viral epidemics of HIV, HBV, HCV and HDV and between their local management. I will confront my own experience and what I have understood of this epidemic in France to a selection of the international literature to propose what, I believe, could improve the care not only of hepatitis but of DUs themselves.

2. A scientific look at the HCV epidemic among DUs

An attempt at understanding the HCV epidemic can be considered as an object of science and discussed as such.

2.1 What is known of HCV hepatitis?

Our knowledge of HCV has grown tremendously since its discovery in 1988. However, gray areas persist. To develop effective control strategies, it is crucially important to determine how epidemiological significant organisms infect us, what is their natural history and what efficacy for its treatment. In most cases these evaluations are not easy.

2.1.1 HCV transmission among DUs: A reappraisal

In 2008, Rhodes et al. observed that "there was much confusion and uncertainty concerning HCV knowledge, including its medical and transmission risks" among drug injectors. Most IDUs viewed HCV prevalence as high and HCV transmission as an inevitable consequence of injecting, HCV risk was perceived as ubiquitous and unavoidable" (4). Is this confusion and uncertainty to be assigned to the messages they receive or our limited understanding of this disease and of its communication?

2.1.1.1 Drug use and HCV: the mystery of the contamination of non injecting drug users (NIDU)

The discovery of HCV followed a search for a viral cause of the remaining post-transfusion hepatitis after HBV had been excluded. Injections make a difference:

- Blood borne transmission through syringe and needle sharing (NSS) has never been questioned and the evidence linking drug injection and NSS to HCV infections are overwhelming. However the level of infectivity of the HCV containing blood remaining in a needle or a syringe after injecting is not known. It is likely that the viral load will be a limiting factor and it is obvious that HCV is able to survive in the environment but we do not for how long? HCV infection is robustly associated with the duration of injections, the number of receptive injecting episodes and of needles and syringes exchanges (NSS), but despite these associations, IDUs may remain hepatitis free after years of risks and others may be contaminated after a unique exchange The observation of Smyth and al. that accidental and unnoticed sharing of injecting equipment may be an important contributor to an IDU's increasing risk of infection over time (5) tallies with my own experience.
- The incidence of contamination through other drug paraphernalia is still debated. Cross-sectional studies have given conflicting results, but cohort studies were able to show significant relations between HCV contamination and sharing drug cookers and filtration cottons among IDUs who did not share syringes (6,7).
- Despite a much higher HCV prevalence (35.3 %) in non injecting drug users (NIDUs) than in non-drug users in some studies (8), the role of equipment (straws, bills, pipes,…) in HCV transmission remains unclear since statistical correlation has never been consistently found, since some misclassification of previous injectors could have occurred and since other possible modes of contamination such as tattooing or sexual transmission were often present (8). However, in some other studies, this prevalence was in the low range observed in individuals living in the same household as HCV carriers. Since it is obvious that every contact is not infectious, a comparison relating their number, the state of the nasal and buccal mucosa (cocaine, heroin) and the lips (crack) (9,10) at the time of sharing , as well as the HCV status of the DUS with whom the equipment was shared could help to understand the cause of these staggering discrepancies.

2.1.1.2 Possible modes of HCV contamination: blood but what else?

An early assimilation to HBV and to HIV, led to the hypothesis that HCV was a sexually transmitted disease. In 1990, a study conducted in Barcelona, in an AIDS clinic, found that 11 % of the partners of infected drug users and 16 % of the partners of infected homosexuals were seropositive for HCV (11). In 1999, using HCV genotypes, Neumayr et al., exploring heterosexual transmission of hepatitis C, finding no other cause of contamination concluded that sexual intercourse could be the cause of contamination in half of the cases (2,5 %) despite any significant relationship with any sexual practice (12). The same year, a metaanalysis computed an order of 1-3 % probability of being found infected among sexual partners of HCV carriers with no other known risk of contamination. The authors had no clue to counsel on their sexual practice viremic HCV carriers with a long term relationship who had not transmitted their infection (13). Overall, since the allocation of these contaminations to sexual intercourse was not significantly related with any history of particular sexual practice, room is left for other possible but never proven modes of contamination such as sharing razor or toothbrushes or, once every other suspected modes of contamination have been excluded, the mysterious "household" transmission (14).

Recent studies rediscovered the risk of sexual transmission among men who have sex with men (MSM) with high-risk sexual behavior (15–17). The HIV epidemic with its mortality and its transient behavioral changes may have hidden its existence for a while, but a Canadian cohort study of HIV positive MSM was able to trace their first contaminations to 1996, with an increase in the incidence of HCV contamination from 0.9 to 2.2 per 1000 person-year to 23.4 and 51.1 % in 2007 which could be related to an increase in the HCV prevalence among MSM as well as an increased level of risks taken during sexual intercourse (18).

Needles are used to perform tattoos and piercings. They are an obvious risk of transmission of HCV and they have been involved in small epidemics. Today, sterile material is used in professional parlors. Thus it is not surprising that non professional tattooing may be associated with a significant risk of HCV transmission among high-risk groups (19). However, like snorting drug, these contaminations, if possible, remain epidemiologically marginal when compared with NSS (20).

2.1.1.3 New insights and new tools could change our understanding of the HCV epidemic

- A consensual belief that HCV antibodies can always be detected years after a contamination has been recently contradicted. If a previous contamination with HCV gives usually rise to antibody production (humoral response) 45–68 days after HCV infection, the presence of a cellular immunity in absence of antibodies has been known for more than 10 years but its epidemiological implication has been ignored until recently (21,22). The discovery that some acute HCV hepatitis could occur and be spontaneously cured without any detection of anti HCV through sequential studies of new expositions has confirmed this hypothesis. It was observed in as many as 33 % of RNA positive cases (23). HCV has also been found in the liver or lymphoid tissue despite the absence of detectable HCV RNA and, even, of HCV antibodies. These occult infections could be the cause of some cases of persistently elevated transaminases (24). However, the clinical meaning of these silent forms which include persistence of HCV in the tissue after clearance of HCV viremia is still a subject of debate (24,25). There was no difference in the prevalence of HCV markers between family members of patients

with occult HCV infection and family members of patients with a chronic hepatitis C (26).

Among IDUS different profiles have been described: but existing data are too scarce and sometimes contradictory to decide what is the real occurence of these evolutions:

- In IDUs engaging in risky behaviors for years without being infected by HCV, the prevalence of HCV-specific T cell response was significantly higher than that of healthy controls in an English study (58/19 %, p=.004) (27). In another study, this response reached 62 % of at risk IDUs lacking antibodies (28). The authors report a 100 % positive response for subjects who indicated that they had shared syringes during the previous 6 months as compared to 50 % who had not, implying a possible disappearance of cellular immunity with time.
- The studies of reinfections occurring in IDUs followed up with repeated blood testing added a new understanding to the clearance of HCV infections: When the rate of NSS remains high and if the tests are repeated at short intervals, a significant incidence of reinfections is observed with a new clearance of HCV RNA observed in more than 40 % of the cases (29,30). It confirms the well known notion of an absence of a total protection by a previous immunization against HCV, as well as the possible immunity in some cases (31,32), but points out a high prevalence of repeated HCV clearance which was not known.
- At last, genotyping HCV core sequences may identify phylogenic clusters and help to better understand HCV transmissions among IDUs and NIDUs (33).

These notions could be of use to explain some of the confusing observation of dissimilar serological status among couples and IDUs with the same risky behaviors in the same neighborhood.

2.1.2 The evolution of HCV chronic hepatitis: A lottery governed by genes?

Currently, HCV, a positive-strand RNA virus distantly related to the Flaviviriadae family, is classified in 6 major genotypes and multiple subtypes. An excellent description of the disease can be found online in the 2004 EMCDDA monography (34).

2.1.2.1 What prognosis for the HCV infections of IDUs?

If some chronic HCV infections progress to cirrhosis, liver cancer and death, this evolution is still unpredictable:

- It is assumed that, after an acute infection, 20 % of the subjects will clear spontaneously the virus. Using antibody screening followed by RNA amplification, 20 % of the cases occurring among IDUs following an acute infection resolve spontaneously (35,36) with a lower clearance rate in HIV infected and African-Americans (37). This prevalence of viral clearance is not significantly different from the general population.
- Progression toward cirrhosis of HCV hepatitis has been studied by two meta-analysis, the second selecting DUs (38,39). The first concluded that cirrhotic progression was comprised between 7 and 18 % after an evolution of 20 years, the second was more precise with a progression rate of 14,8 % with a confidence interval of 7.5 to 25.5 %. Male sex and alcohol consumption added an additional 5 % each. However, when the original studies were independently considered the progression rate could vary from

0.3 to 34.9 %, and the computation was performed using the data of 47 papers selected out of 764 potentially relevant articles and 6 679 abstracts. Significant bias could explain these ranges such as a selection of symptomatic patients or the different proposal to perform liver biopsies and their acceptance. In my own series of 650 DUs recruited through my addiction network and in prison with liver biopsies proposed and performed (acceptance 98 %) whenever HCV RNA was present independently of the level of transaminases, after 20 years, the prevalence of cirrhosis was 10,5 % (alcoholics non alcoholics 3.6 %; alcoholics 12.5 %). In a study conducted in the general population in Italy, HCV infection was associated with a severe liver disease in less than 50 % of the cases (40). In these studies as well as in a study of DUs, a high daily intake of alcohol (3 or more drinks) explained most early progression to cirrhosis in DUs (36).

- The prognosis of post-transfusional hepatitis mortality has been the first to be studied. They are characterized by their high rate of early death, their old age at contamination and the one-shot infection. It is believed that infections occurring at a younger age have a more benign evolution. Nurses infected by contaminated gammaglobulins had a 1 % prevalence of cirrhosis with no death after 25 years (41). This benign evolution has been confirmed by others (42). In 5 transfusion retrospective studies, 25 years after exposure all-cause mortality was not different between cases with an history of acute hepatitis and controls and the liver-related death significantly higher than controls was lower than 3 % (42). 16 years after contamination, a national cohort had no excess mortality compared to controls, but the risk of death directly from liver diseases was higher (Hazard ratio: 2.71, 95% CI 1.09-6.75). An excessive alcoholic consumption was present in 30 % of those deaths (43) Progression after 20 years is "less" known but the overall mortality of HCV liver diseases is usually considered to be in a range of 20 to 30 %. The higher rate of death observed among veterans. infected by HCV by Butt et al in 2009 could be related to the presence of other comorbidities such as alcohol, tobacco, violence… since the cause of death was not recorded (44). However, modelisation of the impact of C hepatitis treatment on patients' survival should consider the high rate of other causes of death among IDUs. They represent a significant proportion of infected people (44) : In a cohort of acute HCV hepatitis followed 25 years, if 8 % were cirrhotic, the death rate by overdose was eight times higher than the risk of dying of a liver disease (45) suicide, violence are common and, in older DUs, cardiovascular or pulmonary diseases compete with HIV and HCV (46–4).. In a more recent study conducted in of long-term heroin addicts in California, premature mortality was high, but "only" 14 % of the deaths were related to liver diseases (50).

A search of prognosis markers of progression in hepatitis C has led to the identification of modifiable and non-modifiable factors which influence its evolution. An older age at infection, a longer evolution, being male or African-American (cancer), viral genotype 3 are non-modifiableOn the contrary, an alcohol consumption greater than 30-50 g/day, smoking (cancer), iron overload, coinfection in HBV and/or immunocompromised HIV positive patients, presence of a metabolic syndrome (obesity, steatosis, insulin resistance) can be acted upon to improve individual prognosis (51). More recently, a search for more accurate predictors of progression to cirrhosis led to genome-wide association studies (GWAS), screening the entire human genome. They identified single nucleotide polymorphisms (SNP) which are not often responsible for functional effects but serve as tag for the causal variant that is not genotyped:

- The study of patients resistant to HCV infection has shown that multiple independent protective genetic factors could explain their diverse evolution: clearance of HCV remaining anti HCV positive (52,53) and "protection" against HCV without production of antibodies (53).
- A link between fibrosis progression and genetic predisposition has been considered after the observation of familial clusters of HCV-related cirrhosis (54). An independent GWAS identified a genetic variant, already associated with alcoholic and non-alcoholic fatty liver disease (55), associated with steatosis and fibrosis severity in HCV related hepatitis (56). The screening of host genetic factors has led to a selection of seven single-nucleotide polymorphisms used to compute a Cirrhosis Risk Score (CRS) which could be able to stratify patients' cirrhosis risk prior to liver biopsy (57). This CRS was able to predict progression to cirrhosis in male patients at a F0 stage of fibrosis, result which could lead to treat them early without having to wait for the development of a significant liver disease. The prognosis value of the CRS held true even in patients who abused alcohol (58).

2.1.2.2 Coinfections of HCV hepatitis with other viruses have worse disease progression and outcome

Since high risk practices are common among IDUs, concomitant or successive contaminations by HBV, HCV and HDV, as well as HIV may be observed:

- HBV is a partially double stranded, enveloped DNA virus of the Hepadna family and HDV is a defective RNA virus which requires the presence of an active HBV infection for its multiplication. The evolution of coinfections is dependent of the innate and adaptative immune host response. The results of their interactions are unforeseeable, but it seems that the newcomer will act as a dominant virus which can lead to the clearance of preexisting infections. Acute HBV, HDV or HCV coinfections or superinfection of HBV or HCV may be the cause of fulminant or subfulminant hepatitis. These interactions may also lead to occult, serologically silent HBV or HCV infections. Coinfections are believed to result in worse disease progression with a higher risk of cirrhosis and hepatocellular carcinoma when compared to HBV or HCV alone (46,59,60).
- Up to one-third of HIV-infected patients are infected with hepatitis C virus. The advent of Highly Active Antiviral treatment (HAART) has transformed the prognosis of HIV infected patients with the occurrence of significant liver related death related to the prolongation of their life expectancy. A meta-analysis of 17 studies including 3567 individuals confirmed that chronic hepatitis C outcomes are worse among coinfected individuals with a prevalence of cirrhosis of 49 % (40 to 59 %), twice the rate observed in monoinfected patients (21 %; 16-28 %). This acceleration is mainly observed in immunocompomised patients and could be acccentuated by an immune reactivation occurring after the introduction of HAART. On the other hand, HAART might lessen progression of chronic liver disease and improve response to anti-HCV therapy without fully correcting the adverse effect of HIV infection on HCV prognosis (61-63) . If hepatic side effects of antiretroviral treatments are common, they do not seem to have a significant effect on the progression of liver fibrosis (64).

2.1.3 Hepatitis C management: Toward a potential Copernician revolution (at a price)

2.1.3.1 Less invasive diagnosis tools

Medical tools have also evolved with less invasive tests for the diagnosis and the follow-up of HCV hepatitis:

- Individuals who perform a test are eager to know its result without waiting for days. Blood access of IDUs is often problematic. Rapid tests answer these problems. After HIV, they have become available for HCV diagnosis. They can be performed using saliva, whole blood, serum or plasma. The frame of their use is controversial. In France, they can only be used by healthcare professionals with a complementary traditional test as confirmation. In the United-states where HIV auto-tests are available, in a DTP 24 % of preferred to remain anonymous, preference which reached 38 % if the test was free (65).
- To detect an ongoing infection, an amplification of the viral RNA is performed which is prone to contamination and false positive results. HCV core antigen detection, easily automated, and requiring less technical skill, has been advocated. Its limitations are noted in some HBV/HCV coinfections (66–68).
- Liver biopsy is often believed to be dangerous and painful by some patients and most general practitioners becoming a barrier to the care of hepatitis C patients. Non invasive tests are proposed: either scores computed from the results of different blood tests or a measure of the elastance (fibroscan) of the liver. Diverse algorithms have been proposed to improve their results but they are today an indisputable alternative to liver biopsy even in HIV/HCV coinfected patients (69,70). The fibroscan does not need a blood sample and gives immediate results (71).

2.1.3.2 Treat all, cure all?

- For 10 years, the treatment of HCV hepatitis has been an association of a long lasting form of alpha interferon with ribavirine. It is able to reduce significantly HCV related mortality (71) Today, there is a clear-cut difference of the response rate to treatment between the types of HCV viruses. Among the 6 genotypes, 2 and 3 need only 6 months of treatment with 80 to 90 % sustained viral response (SVR) whereas, genotype 1 and 4 usually need 12 months for a SVR of 50 %. Response rate of DUs are in the same range as the general population (72). Our finding of a significantly better SVR of genotype 1 infected DUs treated by buprenorphine as compared to methadone remains to be explored in a prospective study exploring that difference (73). An “à la carte” adaptation of the duration of treatment has been proposed for genotype 1 following the time of RNA clearance at 4, 12 or 32 weeks followed by respective treatment duration of 24, 48 or 72 weeks which has been confirmed for HIV/HCV coinfections (74,75). For patients with advanced diseases, treatment has been completed thanks to the use of growth factors which improved their tolerance (76)).
- This individual response could be predicted before treatment prescription: A better knowledge of the immune response against hepatitis C gives a central role to regulatory T lymphocytes which are present in the necroinflammatory infiltrate of the liver. By studying a single nucleotide polymorphisms (SNPs) linked to the IFN-lambda 3 (IL28B) gene it is now possible to predict a better prognosis for patients infected with genotype 1 with the CC genotype. They are more than twice as likely to respond to 48 weeks of treatment than non-CC genotypes (CT,TT) (77,78). This association has also been found in hepatitis C virus genotype 2 or 3 patients (79) and in HIV coinfected patients (80), but not in genotype 5 (81).

- However, new drugs which have been specifically tailored to HCV will improve these results. The first antiproteases on the market, Telaprevir and boceprevir improved the SVR for genotype 1 from 50 to 70 % for naïve patients and improved significantly SVRs of previous relapsers or non-responders (82,83). Since these drugs are added to interferon/ribavirine side–effects are more frequent and severe with serious cutaneous reactions (telaprevir) or a need for more growth factors (boceprevir). Early responder could benefit of shorter treatments. Other drugs are in the pipeline which could still have better results. The combination of two antivirals to the association of interferon/ribavirine led to a 100 % viral response, 12 weeks after the completion of treatment in previous non responders of a classical bitherapy. In a near future, association of 2 antivirals tailored for HCV should be able to cure almost every infected patient. This improvement has a cost: A full treatment course of telaprevir (12 weeks fixed-duration) will cost £30 000, whereas a full treatment course of boceprevir will range from to €22 000 to €40 000 (84) which should be added to the €16 000 of 48 weeks of bitheray by interferon and vidarabine for a genotype 1 (for a genotype 2 or 3, 24 weeks of a classic bitherapy are usually sufficient) and to the €1 000, annual cost of the care. The latest communications in international hepatology meetings promise a second generation of antivirals more effective with less side-effects which could be used in association without interferon and, in some cases, ribavriine in a near future. They should be able to cure almost all the hepatitis whatever their genotype. We do not know yet what will be their cost.
- Among HCV/HIV coinfected DUS at risk for liver disease progression a combination of interferon and ribavirin, is not highly effective; it has lower rates of SVR than monoinfected patients, especially for coinfected patients with HCV genotype 1 and those of African descent. Direct-acting antivirals might overcome factors such as immunodeficiency that can reduce the efficacy of IFN with the additional problem of interaction with antiretrovirals which should lead to early treatment independent of the stage of the liver disease, before the introduction of an HIV antiviral treatment (85).
- Most of the infectious epidemics observed in humans have been controlled by vaccination campaign. Novel vaccine candidates have been studied based on molecular technology such as recombinant proteins (E1 and/or E2 glycoprotein), poly peptides, virus-like particles, plasmid DNA and recombinant viral vectors which can be combined with novel adjuvants. Some of them have reached Phase I/II human clinical trials with, in some cases, production of robust antiviral immunity but the challenge is to move to test their efficacy in at-risk of infected population to prevent new infections. Their cost has led to preferential studies of their efficacy as adjuvant for existing treatment (86,87).

2.1.4 Conclusion: DUs confusion and uncertainty are founded (they are not alone in that situation)

We may know for certain that HCV infection follows conditions or practices causing blood transmission whether through contaminated needles or through mucosal traumatism and/or bleeding during hetero or homosexual intercourse. However, the studies of HCV transmission explore only the expected associations the researchers believe to be relevant. One must be cautious not to mix up low statistical significant association with causal

relationship and remember that our inability to explain some HCV contamination may be related to, until now, unknown or overlooked modes of contamination: Animal bites were found significantly related to HCV infections (88) and a model of transmission of HCV by biting arthropods could explain the maintenance of long-term endemic transmission of HCV in Africa and South-East Asia (89). The route of contamination of patients on hemodialysis has not yet been understood leading to a debate on the interest of their isolation (90).

Today, our prevention messages are "simple"!!!:

- Do not inject and if you do, never share syringes, needles or any injecting paraphernalia.
- Never share bills and straws you use for sniffing or pipes you use to smoke cocaine.
- Use condoms for every sexual intercourse.
- Choose a reliable professional to perform your tattoos or piercings
- Never share your toothbrush and your razor.
- If, despite these counsels, you have taken some risks make a blood test.
- If positive for HCV, ask to be treated.

But, even if a DU could follow these very restricting recommendations, it is not possible to guarantee an absence of contamination. Confusion and indetermination are not gone. We are not on the eve of a simple training course for professionals as well as for the public at large which would explain hepatitis C and give coherent and always effective recommendations for prevention. We have to wait for effective vaccines.

2.2 The epidemic of HCV hepatitis among DUs is not controlled

More than 20 years after the discovery of the hepatitis C virus, much of the ongoing epidemic is attributable to unsafe drug injections. An evaluation of the drug consuming population and of the DUs infected with HCV is recognized as an arduous exercise. One can consider snapshots taken at one time or can study a trend in a cohort. Both approaches must consider the evolution of:

- The population of DUs and the nature of drug consumption. Younger addicts cannot be treated as the older ones minus ten or twenty years. The French OFDT study "le matos" (the works), interviewing a panel of injectors, has been documenting these changes since the nineteen seventies. These different attitudes may coexist in different age groups (91). Despite globalization, each country and, even, each region, has its own history and market. I have described its course in France in a short overview in 2007 (92). A series of publications relevant to the French drug consumption can be downloaded from the site of the Observatoire Français des Drogues et des Toxicomanies (OFDT) in free acess (http://www.ofdt.fr/ofdtdev/live/publi.html).
- Illegal drugs' use has cycles. Cocaine will succeed heroin, designer drugs will find a new public. A new drug is detected each week in the European market (93). Recently, high levels of amphetamine injection have been reported around the Baltic, as well as Slovakia and Hungary…. A tremendous growth of the drug business occurred since the beginning of a war on drugs and the repressive laws of the 1970s. It is related to the huge profitability of the trafficking and the increasing demand of new consumers for psychoactive drugs, licit or illicit.

2.2.1 How many (intravenous) drug users and what proportion is infected by HCV?

Despite these recognized problems, figures are none the less produced: in counties of Western Europe, HCV prevalence among IDUs fall in a range comprised between 47.1 % (Austria) and Netherland (86.2 %) (94). The number of infected DUs in Western Europe could reach 727 500 (95% CI 497 000 – 1018 000).

France is the only country were different approaches have been used at different times to estimate the number of DUs and of people infected by HCV. A comparison of their results gives an idea of the accuracy of these estimations:

- The OFDT recently produced and discussed an estimation of the prevalence of problem drug users in France following a methodology shared by all the European countries: 5,4 to 6,4 /1 000 hab 15-64 years old. This estimate is almost twice that of Germany but lower than Italy, Spain and UK which had the highest prevalence. It has certain limits which are listed in the publication with a rare honesty (95):
  - First, the changing definition of the subject of the estimate. In 1993, "heroin addicts" were, at least, 160 000. In 1995, the estimate was of 142-172 000 "opiate problem users". In 2006, a new definition, taking into account the change in the drug market, considered "intravenous drug users or regular users of opiates, cocaine or amphetamines", led to an increase of 44 %. The change in these estimates may be more related to a difference in definition than to a real change in the size of the population.
  - Second, the proposed estimate of 230 000 problem users (210 to 250 000) cannot hide the fact that the real range computed through the four different methods before its narrowing by the experts to a definite number, without convincing arguments explaining their choice, was 147 000 to 367 000.
  - Third, these approaches ignored the users who have not been and will not be in contact with one of the information sources used (arrest, treatment, health problems, death, etc.)". For cocaine which is considered to be one of the most "addictive" drugs, no more than 20 % of users become addicted after 20 years of use, 80 % may not be accounted for by these evaluation (Wagner 2002). This statement is of importance, since this population is not negligible and can influence the evaluation of the number of patients infected by HCV through their drug use (96,97). In the nineties, most patients 30 to 40 years old, carriers of HCV, who came in our unit without any history of a possible contamination, confessed that 10 years before, on one or two "festive" occasions, they had injected drugs with friends and shared their syringes. They were not "addicts" and they did not consider themselves as such.
- The Veille Sanitaire (VS), the French organization studying public health, conducted 4 different surveys leading to four different results:,
  - Starting from HCV prevalence in the general population, two successive studies were conducted ten years apart (1994-2004) (98,99). Both addressed people covered by the French public welfare system (only 9 % of the recruited population agreed to make a test. They differed only by their scope. The second being much larger than the first. The interval of the first estimate was 500 000 to 600 000. Among IDUs, HCV prevalence was 78 %. Ten years later, what was presented as a more accurate

estimation of 367 000 was given with 65 % of viremic patients. The only explanation given to this spectacular decrease was the better methodology of the second study. Among the 0,38 % who recognized a previous history of injecting drugs, HCV prevalence was 55,5 % which would lead to a total of 150 000 French people with an history of at least one drug injectors in 2004, 82 500 of whom would be infected by HCV.

- In 2003, the number of DUs infected by HCV and of the incidence of new contaminations started with an hypothesis of a number of active injectors ranging from 80 to 100 000, given, at the time, by the OFDT and a prevalence of 60 to 70 %. The proposed number of infected IDUs was 48 000 to 70 000 and the number of new infections ranged from 2 700 to 4 400 for an estimated yearly new contaminations of 11 % (100).
- The fourth study was a cross-sectional multicenter survey of DUs having injected or snorted drugs at least once in their life conducted in 2004, the same year as the second population prevalence study (101). It was a two stage random survey of DUs selected to represent the diversity of drug use. Fingerprick blood samples were collected on blotting paper in 75 % of the screened population. The overall prevalence of HIV and HCV were respectively 10.8 (0.3 % under 30 years of age) and 59.8 % (NIDUs 27.9 %; IDUs 73,8 %; under 30 years 28%). In multivariate analysis, factors independently associated with HCV seropositivity were age over 30, HIV seropositivity, having ever injected drugs, opiate substitution treatment (OST), crack use, and precarious housing. HIV seroprevalence was not related to an history of injecting, but increased with age with a geographic difference of prevalence.

Contrary to the OFDT, no explanation was given of these discrepancies: a decrease of one third of the number of people infected by HCV between 1994 and 2004, and, the same year, 2004, a discrepancy of 18.3 % between two estimations using different methodologies to assess HCV prevalence among IDUs.

2.2.2 Is it possible to know HCV prevalence and incidence among DUs and what is the efficacy of harm reduction programmes?

2.2.2.1 Cohorts the incidence and risk factors of new infections can only be studied in cohorts of IDUs initially seronegative

Ideally, these cohorts should begin when IDUs start to inject and no drop out should occur or, at least, the drop outs should not differ from the rest of the cohort. Of course, these requirements are almost impossible to fulfill. In some cases, infection incidence rate was even computed from a retrospective selection of patients who had at least two serum samples available and found initially seronegative (102–104). In a prospective study in the north and east of France, 28.6 % were lost to follow-up and differed significantly from the others who remained in the study (6). These studies can inform on the modes of contamination. They can never accurately predict the true HCV incidence among all the DUs. However, the incidence rate of new HCV contaminations among NIDUs remained low in the few cohort studies which included them: 1/422 (0.4/100 PY (95 % CI 0.0-1.2) (105), none in those who did not start injection (106).

The four randomized studies of the impact of interventions to prevent hepatitis C infection among IDUs were not able to show significant differences (106–108). Despite an exclusion of severe psychiatric or somatic illnesses, which represent a significant bias, the drop-out rates were high. For example, Abou-Saleh et al. explored behavioral interventions among DUs already followed by drug treatment services. Among the 206 IDUS (initially 1354) who remained after exclusion of HCV positivity, of severe mental or physical illnesses or serious legal problems, 54 % refused or dropped out during the inclusion process, 95 were randomized, 82 % and 65 % were followed at six months and 12 months. In a per-protocol approach, the rate of contamination was higher at the end of six months (18 %) than after 12 months (12 %) and there was no significant difference between the two interventions even if the trend was "in the anticipated direction" (108). In an intention to treat, drop-outs would have been considered as possible contaminations raising the contamination rate over 50 %.

Hagan et al. (109), mixed up these studies with different other interventions from bleach disinfection of syringes to behavioral interventions, in a report with strong methodological bias. First, the majority of the 26 studies were not intended to assess the efficacy of an intervention but to measure the rate of new infections among a cohort of IDUs. Then, they included the univariate odds-ratios of seroconversion even if they were not retained in multivariate analysis. For example, in the French study, a 60 % reduction in HCV incidence was observed between the patients treated with oral substitution treatment (OST) and the others. However, once the level of cotton and syringe sharing were included, this difference disappeared because these levels were not equally distributed between the two groups.

These observations explain why the quality of evidence of intervention impacts is found to be lacking and why it is so difficult to prove the efficacy of any harm reduction procedures. At best they can show that DUs retained in a programme fare better than those who stay outside or who quit. But they cannot prove that the decision to take part in the programmes does not select less risky behaviors and, most of all, that the proposal of these programmes to every DU would result in a significant decrease of new contaminations, which, of course, should be their aim.

2.2.2.2 Cross sectional studies

The results of repeated cross-sectional studies have the advantage of not being dependent of the retention rate in a programme. However, the population recruitment must be representative of the population studied and its modalities must not change from one period to the next. An incidence survey has been added to the cross-sectional approach in some cases. The community based study by Mehta et al. in Baltimore (110) and the study of IDUs attending Needle and Syringe Programs (NSP) in Autsralia by Falster et al. (111) can be considered as models:

- Mehta et al. studied a cohort of IDUs initially recruited in 1988-1989 and then added new IDUs in 1994-1995, 1998 and 2005-2008. They followed those who were seronegative for HCV and HIV and compared the new recruits. They observed a significant decrease in HIV infection from 5.5 cases/100 patient/year in 1988-1989 to 0/100 py in 2005-2008, whereas there was no significant change in HCV incidence. The prevalence study observed a decline in HCV prevalence among the youngest (39 years) and those who had a shorter injection history (<15 years). An increase in the duration of injection to reach a 80 % prevalence was observed between 1988-1989 (5-9 years) and

2005-2008 (15-19 years). After adjustment for demographic and time since injection, significant differences were observed between HCV prevalence in 1988-1989 and 1994-1995 on one hand and 2005-2008 on the other. A small proportion of this decline was explained by changes in drug-related risk behavior over time. It could be the consequence of a decrease of HCV prevalence.

- In Australia all IDUs attending a NSP site participating in the study were invited to complete an anonymous questionnaire and to provide a capillary blood sample (participation rate: 41 to 61 %) every year between 1995 and 2004 (Falster 2009). After adjustment for covariates, HCV antibody seropositivity remained associated with a longer duration of injecting, older age, participation in the state of New South Wales, opiates as the last drug injected, imprisonment in the last year, female sex, daily or more frequent injection, sharing needles and syringes in the last month, sex work, and survey participation in 2000–2004. An increase in HCV prevalence was found within injection initiation cohorts over time, with prevalence appearing to reach saturation around 90% in the older cohorts. An increase from 1895-1996 to 2003-2004 in the prevalence of HCV infection among IDUs who had injected less than 7 years could reflect an increase in the prevalence of HCV in that population.

2.2.2.3 France and Lyon: the course of an epidemic

Knowing the methodological limits of any evaluation of an HCV epidemic among DUs and of the effectiveness of harm reduction programs, I will present the results of the studies I conducted in Lyon and in France and, taking into account the other French evaluation on the subject and my experience of thirty years of care to DUs, I will give a tentative interpretation of the course of the epidemic in France.

2.2.2.3.1 Prison

I conducted studies in Lyon's prison because it was the only place, outside of complex snowball enquiries, were no bias was met, in the recruitment of IDUs, which could be related to a care demand. Every IDU entering Lyon's prisons between 19987-1989, 1997-1999 and 2009-2011 were asked to answer a questionnaire and to provide a blood sample. Acceptance was high (>90 %).

- Among DUs entering prison, before 1990, injection was the rule (90 %) and heroin was the main product. This study showed a sharp decrease of "indiscriminate" sharing from 65 % for those who had begun their drug use before 1980, to 15 % for those whose first use began after 1987. This change was related to the occurrence of the AIDS epidemic in 1984-1985 and predated the free access to sterile needles and syringes of 1987 which, nevertheless, had an additional impact. After 1985, an increasing number of pharmacists agreed to sell syringes answering an increasing demand of IDUs. Follow-up studies conducted in the same environment among injectors confirmed this trend in the change of behavior and of viral prevalence with a quasi disappearance of indiscriminate syringe sharing after 1992. Conversely, the absence of any sharing reported by less than 5 % of IDUs who had begun to inject before 1980, reached 70 % after 1990.
- In 2009-2010, a radical change in drug consumption had occurred from heroin injection associated by less than 10 % of DUs to cocaine in speedballs in the eighties to an almost equal number of heroin and cocaine consumers (cocaine 82 %; heroin 70 %; 52,6 % used

both drugs). Only one fourth had injected. These results underline the change in drug use observed at a national level (95). The prevalence of injection was higher (29.5 %) among heroin addicts than among cocaine abusers (18.3 %) but, among injectors syringe and needle sharing was not different. There was no difference in HCV prevalence between non drug users (2.4 %) and NIDU (3.9 %, OR 1.7 95 % CI=0.7-4.2). This prevalence rose to 48.6 % for IDUs who said they had never shared their needles (OR/NIDU 23.9 95 percent CI=8.0-65.8) and to 66.7 % for those who had (OR/NIDU 44.7 95 percent CI=13.6-167.4). HCV detection was also related to an older age and a longer drug use but had no relation, among injectors, with the nature (heroin or cocaine) of the drug used. One fourth (24,4 %) were nationals of countries belonging to the exUSSR which is in accordance with a trend observed in most French hepatitis units for some years.

- In a comparison of IDUs entering prison in 1987-1989, 1997-1999 and 209-2011, the decrease of syphilis infections among that population as soon as 1986 (11 % before to 4.7 % after) and its disappearance after 1990 demonstrated the decrease of the trade of sex for drug. In a multivariate analysis controlling for date of first injection, duration of injection, place of injection (for HIV alone) and risk sharing the Odds ratio of viral infection in 1987-1988 compared to 1997-1998 were 15,4 for HIV, 7,8 for HBV and 3,3 for HCV, indicating a decrease (certain for HBV and HIV, possible for HCV) in the prevalence of these infections among injecting drug users. On the contrary, no difference was observed between 1978-199 and 2009-2011.

2.2.2.3.2 Multicenter cross-sectional studies

In 1996 a multicenter study, at that time the largest state funded study of DUs, recruited 1302 DUs in 3 French towns (Lille, Lyon, Paris) among GPs and their referral hospitals. 120 data were collected. It confirmed the trend observed in Lyon's prison with a decrease of the indiscriminate needle sharing. A consistent increase in age for first drug use since the end of the eighties was observed. Before 1981 and after 1991, the prevalence of syringe sharing without precaution was divided by 8 while that for spoons was only divided by 1.4, for cotton wool by 1.6 and that for back loading by 1.3. Needle sharing was more frequent at night (60% versus 30 %). The proportion of nightly exchanges increased during periods when patients were "high" (59%), during withdrawal (61 %) and at the time of a relapse (76 %). This sharing at the time of relapse was unpredictable and represented approximately 25% of cases. Shared material other than syringes were in decreasing order: spoons (46%), filtration cotton (39%) and 'back loading' (20%). 9 years after the legalization of the purchase of needles and syringes in pharmacies and 5 years after the opening of the first NSP in Paris, a very small proportion attended NSPs (7%) or vending machines (2%). Socio-economic variables were not associated with the extent of needle sharing (a continuous professional activity was only found in 20% of cases but only 3% of drug addicts in this study did not benefit from any kind of social assistance). Gender, living with a partner and housing were not significant. Only the level of education and, to a lesser degree, professional situation was of importance. The prevalence of needle exchanges without precautions decreased from 29% in users who had primary level of education compared to 12 % in those who had started high school. Prostitution was seldom reported by men (3 %), but 29 % of women recognized this practice which declined from 33 % before 1980 to 21 % after 1990, most frequently observed in occasional "hookers" (28 to 16 %). The prevalence of cutaneous abscesses (23 %) and of overdoses (29 %) had not changed with time.

2.2.2.3.3 Discussion

These studies confirmed the disappearance of the HIV epidemic and, on the contrary, a persistence of the HCV epidemic. This observation is concordant with the results of national surveys. In 2008, the estimated French total number of new HIV infections among IDUs was 70 (95 % CI 0-190) with, for the first time, a majority of DUs newly discovered being born abroad (112)(Levu 2011). A credible story can be told:

- Before the AIDS epidemic, if hepatitis were known to be present among DUs, they was ignored since their symptoms were few, no treatment was available and their death rates (fulminant or subfulminant hepatitis) were exceptional, much lower than those of deaths by overdoses, violence or suicides. With the sudden onset of the HIV epidemic, everything changed. DUs wasted and died and as soon as 1984-1985 everybody knew that AIDS was an infectious disease transmitted through sexual intercourse and blood transmission. The message had all the characteristics which make a message "stick": it was simple (HIV infection led to death), unexpected (people paid attention), concrete (it was understood and remembered), credible (people agreed and believed), emotional (people cared) and led people to act (a credible story was told with a solution: condoms and sterile works). Paraphernalia use (the impact was obvious on needle and syringes, filters were mostly ignored) as well as sexual practices changed significantly. I observed a decrease in NSS which begun well before the law of 1987 on the free access to needle and syringes, sex for drug and the prevalence of syphilis declined at the same time and, furthermore, DUs died (those who took the most risks). As a result, the HIV epidemic disappeared in regions like Lyon were its prevalence had been low when the epidemic was discovered. In others (Paris, Bordeaux, the south of France), a small pool of DUs infected with HIV survived. They were slow progressors and were able to access HIV infectious specialists and wait until HAART were available. They remained a reservoir for some occasional contaminations (the respective role of injection and homo or heterosexual transmission in these new infections is unknown). This is in accordance with our multicenter study of 1996 and explains the discrepancy between the high rate of HIV prevalence observed in Marseille and the national observation of a very low incidence of new infections (113). Contrary to Jauffret-Roustide (101), I believe that the difference in HIV prevalence between Lille and Marseille in 2004, is not mainly related to a prevalence of injection, which was not significantly related to HIV seroprevalence in their survey, but to a difference in the course in the epidemic shown by our 1996 study: Marseille had already one of the highest HIV prevalence in the early eighties and the explosion of drug use in Lille occurred in the late eighties, when people were aware of the HIV epidemic, explaining the constant low HIV prevalence. However, recent changes are observed with the occurrence of new cases coming form countries were HIV prevalence is high among IDUs (today countries from the ex-USSR, maybe Africa were drug use is expanding tomorrow). The impact of this new epidemic on native DUs is still unknown.
- The course of the HBV epidemic followed that of HIV. To be infected, one must encounter a infectious carrier: 90 % of adults newly infected will spontaneously clear the virus and only a fraction of them will be infectious through sexual contacts and through NSS. If in the eighties and most of the nineties, a diagnosis of infection through drug use could be made when HBV together with HCV markers were detected, it was not the case anymore after 2000, or earlier with younger addicts only infected with

HCV. HDV, which needs an HBV coinfection, had disappeared at the end of the eighties, but comes back, sporadically, with eastern migrants.

- For HCV, the course of the epidemic is radically different. It is obvious that in the early eighties, HCV, like HBV prevalence was high among IDUs, in the range of 80 to 90 %. There was no difference between French regions. Harm reduction did not exist. The 3 surveys I conducted before 2000 give a coherent picture of their evolution. Before the discovery of the AIDS epidemic, the majority of IDUs took no precaution with their "works" (even if they injected only once in a recreational setting). Since most IDUs were infected the first year of injection, HCV prevalence among IDUs with an history of only few injections did not differ significantly from that of those who had been indiscriminate. A decrease in NSS occurred in the eighties resulting in a delay when duration of injection was considered, but the influence of the level of NSS, when it had occurred, was not significant, reflecting the persisting high HCV prevalence. The 1996 survey emphasizes the low access to harm reduction programs such as NSP or vending machines at a time when most of the changes in the course of the HIV and HCV epidemic had occurred. NSS occurred at a time when pharmacies were closed, at a place where vending machines were absent and when a sudden craving was felt. Behavior reported by most of the few IDUs I followed who seroconverted. This situation was not exceptional in DUs receiving OST after 1996. A small but significant trend was noted toward a reduction in the epidemic when comparing IDUs who had begun injecting before 1990 and between 1990 and 1999. This decrease was sustained in 2009 but the size of the sample is too small to make final conclusions. However, differences may exist between French regions. In Alsace, in a GP network, HCV prevalence among DUs under 30 years of age was only 7 % (114). This dissociation in the evolution of HIV and HCV epidemic has been observed in Vancouver (115) and in most countries were drug injection was present before 1980 (116,117).

2.3 From an addition of successive layers of harm reduction to the recognition of the complexity of the control of risky behaviors

A thorough synthesis and evaluation of harm reduction effectiveness has been published in an EMCDDA monograph in 2010 (118) following others (119–121) with the same conclusions: the absence of high-quality review evidence leading to question this efficacy. I will try to consider the respective impact of past harm reduction programmes and the improvement which could be implemented to improve their efficiency in the French context.

2.3.1 Prevention

2.3.1.1 Oral substitution treatment

The massive introduction of OST in France in 1996 was followed by an instantaneous and tremendous change in the care for DUs. In 2002, it was assumed that one third of problematic opiate users (52 000) were engaged in long-term treatment with an additional 22 000 receiving prescriptions on an irregular basis (122). OST introduction occurred at a time when the HIV epidemic among DUs was already controlled. Its impact is, thus, difficult to assess. However, OST in community setting is considered to reduce HIV seroconversion and to have a possible role in reducing the number of HCV seroconversions among DUs who remain in the programmes. From my experience and from the results of a

study of the migration of IDUs inside Lyon's healthcare and penal institutions I conducted in 1989, OSTs have delayed the time of transition to injection among heroin users. But since many other variables have changed during that period, and since we still do not know the evolution of the prevalence of injectors, this assumption remains speculative. The problem which remains is what to do with the non compliant DUs, most at risk of infection or with those who do not attend OSTs? The change in the nature of the drugs consumed by DUs observed in the last years with an increase in cocaine/crack use could limit the impact of OST on these consumers and should lead to an evolution of the DPs even if, recently a disaffection for cocaine and a come-back of heroin through micronetworks of users-sellers (123) has been reported in France.

2.3.1.2 Reduction of syringe and needle sharing (NSS)

The first harm reduction programme implemented in France occurred in 1987 with a law allowing free access to needles and syringes in French pharmacies. The motivation behind this decision, like the decision, in 1996, to offer an easy access to OST, was more a protection of the heterosexual community from HIV and hepatitis viruses than an improvement of DUs' care. For someone who lived that period, it is obvious that, this decision increased significantly a preexisting trend and was significantly associated to a quasi disappearance of indiscriminate NSS among IDUs. From my study in prison and the national survey of 1996 as well as my own experience with the IDUs I followed at that time when no OST, beside neocodion, was available, it is "obvious" that it answered a demand of IDUs and decreased significantly NSS after they had discovered and realized the risk inherent to that practice. Following this first move, steribox containing needles, syringes, filters and condoms have been sold to IDUs for a low price or have been available through NSP which have been opened in the early nineties. In 1998, with an estimation of 2.8 injections per IDU per day, Lurie and al. estimated that between 920 million and 1.7 billion injections by IDUs took place each year in the United States (estimated 12 million in San Francisco and >80 million in New York City) (124). Using the same level of daily injections, with a conservative estimation of 80-100 000 IDUs, 80 and 100 000 million of injections could take place in France. An annual estimation of syringes sold to IDUs in France between 1996 and 2003 made by the INVS increased from 1996 to 1999 (14.7 to 17.7 M) and then decreased dramatically from 1999 to 2003 (10.9 M) (125). This decrease was ascribed to an increase in OST during the same period. NSP accounted for only 1.5 M exchanges with large differences in the number of steribox exchanged yearly (253-10 000) between as many as 129 programmes or vending machines. The observation that a syringe can be reused 10 times is not a surprise. Pharmacies after they began to give free steribox have been shown to quadruple in the first 6 months the number they dispensed to the same number of IDUs (126). In a survey of 35 large metropolitan areas in the US, the range of the number of syringes distributed was 2 per 10 injection events to 3 per 10 000 injection events (127). Sterile syringes for each shoot may be desired, but can this goal be reached and would it be sufficient to prevent receptive exchanges? For cocaine users, distribution of glass stems, rubber mouthpieces, brass screens, chopsticks, lip balm and chewing gum, reducing the harms associated with smoking crack, may decrease the number of injections (128).

Considering what is unknown about the number of IDUs, their access to harm reduction programmes (HRPs), the efficacy of theses HRPs and the modes of viral contamination, one can be surprised that models fitting strategies to control the HCV epidemic can be proposed.

However, models exist even if they are oversimple and if some (many) of their initial assumptions on the rate of viral transmission or the efficacy of NSP and OST to prevent infection, may be problematic. The conclusion that high-risk DUs are infected early and that the rate of infection among low-risk groups will continue for years are truisms (34). Percolation-based approximations can be highly biased when one incorrectly assumes that infectious periods and when deterministic models assume that every contact is with a new individual. Thus, models should be significantly improved, for example, with the use of stochastic models which take into account lasting relationships and inclusion in groups, but they should also use additional data on specific populations (129,130). Despite these limits, Vickerman et al. suggest that, in the UK, NSP and OST have been able to limit 50 000 new infections in the UK, but even with their initial optimistic assumptions, they conclude that a reduction by half in chronic HCV prevalence would need OST and 100% NSP to be scaled up to 80 % coverage for at least 20 years (131).

French results do not support a significant impact of harm reduction programmes on the course of the HIV and HCV epidemic outside of the free access to sterile needles and syringes in pharmacies (112).

2.3.2 Hepatitis treatment

The treatment of DUs' viral infections has been considered since the occurrence of the AIDS epidemic. In the nineteen eighties, our diagnosis tools were limited and available treatments were experimental. In Lyon we used the first anti HBV antiviral in continuous perfusions of four weeks durations for severe HBV hepatitis as early as 1979, then with beta interferon for HBV/HDV coinfections and NonA NonB hepatitis in 1984 and alpha interferon for both since 1989 after the first randomized trials of 1987. This know-how encompassed also HIV infections and at every step we treated active IDUs years before OST could be prescribed (1996) in France. Our recruitment was biased, but we were able to screen and treat most of the DUs who asked for heroin detoxification or hepatitis and HIV treatment. On another level, a national consultation in 1991, concluded that HIV infected DUs did not differ from the other patients. Compliance was related to housing problems whatever the modalities of infection. Having treated DUs for their HIV infections since 1984 and for their hepatitis since 1986, we did not agree with the recommendations of the French consensus conferences which denied the treatment of HCV hepatitis to active DUs in 1997. This position, initially controversial, has become the norm with an emerging consensus that DUs can be treated for their hepatitis on a case by case basis. In a study of the perception of their disease in 2000, 60 IDUs successively entering Lyon's prisons were interviewed. At least one liver biopsy had been performed in 49 (90 % of those whose hepatitis had been discovered more than 5 years earlier). 80 % of viremic DUs who had a significant fibrosis (> F1) had been treated and 50 % of the others on account of fatigue or a desire to be treated. The multi-disciplinary management we developed with success in the early nineteen nineties is now proposed as a possible solution to improve access to treatment (132–134). The possible impact of treating HCV infected DUs on the course of the epidemic has even been studied by different models which are the subject of debates (135,136).

In France when we proposed to study the possibility of treating HCV hepatitis to decrease HCV prevalence in a nationally funded Clinical Hospital Research Programme in 2002, few hepatitis units received IDUs. In 2004, in a national observational study of 40 hepatitis units,

only two hepatitis reference centers treated a significant number of HCV hepatitis of drug users. In 2011, after three successive national plans, the situation has changed. 90 % of the 31 hepatitis reference centers who treat two third of French HCV hepatitis declared that DUs' hepatitis care was a strategic decision. Differences in history and location, as well as the size of the HCV specialist team (range 0.8-10) made each centre a special case. Various innovative solutions have been implemented, in some cases before the allocation of resources. A partnership was present with drug treatment programs (DTP) (85,2 %) and GPs' network (25.9 %). 44.7 % found that care for DUs hepatitis did not need a specific competence. Perceived problems were reported by only 34.3 % of HCV specialists (absenteeism) and 48.3 % of nurses (absenteeism, blood access). Waiting times were similar for DUs and non-DUs. Our results support collaboration between services involved in DUs' care. However their complete and complex integration may only be needed for the most precarious such as homeless adolescents.

3. HCV, drug use, and the world complexity

Biomedical knowledge of the HCV epidemic among DUs is obviously not enough to be able to control its course. My practice taught me that if objectification of DUs as well as of their hepatitis was inescapable, an understanding of its limits implies an integration of other aspects of our "being-here" (Dasein) such as the brain, society, social systems and ethics.

- The "rationality" of one's decision includes his lifetime experience, "being-here". The human brain constructs the world from gestation onward in an interaction with its environment. This process governed by genes and their expression (epigenetic) (137) leads to more and more complex "logical" choices following statistical "Bayesian inferences" (138), the results of which may be forgotten but still predetermine future decisions by limiting the scope of one's expectations. Its integrated complexity is mainly unconscious and organizes a memory which is more concerned by one's future efficiency than by an accurate memorization of past events. It leaves a small place to what we consider as consciousness which has to decide among a limited number of preselections networked through sleep and "mind wandering" (139–142). Brain exercise like meditation could improve its efficiency. The development of the brain is crucially sensitive in its first months and years to its relations with its human environment which will make up the limits of its future "creativity" through the secure basis of its attachment (143–145). At adolescence, the brain restructuration will settle its adult functional frame (146) . Drug use and addiction represent only one dimension of this complex adaptative interaction which cannot be "revolutionized" by a single logical argumentation. The impact of the initial AIDS epidemic, with its massive death toll, observed in France in the nineteen eighties will not occur anymore. It was "one shot". Prevention messages, treatment proposals have to take into account these changing individual ecologies. One can be immediately convinced by the description of the risk of NSS but will nevertheless engage in NSS when its result is an instant improvement in well being compared with an improbable success of hepatitis prevention over the future years of addiction and the high probability of dying before the advent of an improbable liver cancer.
- Modern society, faced with the management of its growing complexity, has organized itself functionally around social systems which rationally objectify the world (147).

They follow an initial selection of their missions through binary codes (health/disease for medicine, presence or absence of an hepatitis for HCV specialists) which makes them "blind" to what has been excluded (the complexity of the world) and gives them a meaning which is the basis of their communication with their environment. These self-referential systems fight to survive and extend their territories responding to stimulations (irritations) of their environment through the limited structural couplings they themselves made possible. Hepatologists will use scientific medical mathematics to modelize the HCV epidemic from scarce and improbable data to convince politics and economics to maintain and, even, increase their funding. Publication of these computations will improve the academic status of biostatisticians. The pharmaceutical industry will fund these studies which secure the outlet of their products and so on. For an hepatitis specialist DU exists first as a carrier of an HCV infection for an hepatitis specialists This practical discovery explains the absence of specificity of DUs' hepatitis management reported by French HRCs: The only limit of HCV treatment was compliance, problem which was not restricted to DUs and, in our French study of HRCs, did not need a specific management for consulting DUs. The question of the control of the HCV epidemic was irrelevant. The global failure of society faced with the problem of drug use and of its management, the awareness of its social complexity are the source of the demand by the professionals of an association in the same place of diverse services addressing belonging to multiple social systems: they would "have to" manage the failures of one particular service which, once its limits recognized, would not be considered as such.

- This organization ignores the complexity of one's "being-here" and is the source of a modern reactivation of the ethical debate (148–151). A DU does not exist as such outside its representation by society's Other. The practical success of HCV care cure but also prevention) is related to the capacity of each individual to recognize and make recognized the inscrutable "otherness" present in every human being. Rational objectification, which is at the core of every scientific approach, is supported by the emptiness of universal concepts which deny this recognition. This otherness is the source of an infinite demand which founds inter human relations. The limited offer which one can propose in return, leaves to this "neighbour", who is to be "loved like oneself ", the freedom to make the right choice. In its absence, the quenching of the scientific rational solution (see Descartes's discourse of a method), when it is implemented, may be transformed into an unbearable violence which will force one to step out of the symbolic order to express one's freedom and say no to an impossible but irrefutable proposal (see paragraph II.1.3.): "death drive" for Freud, "radical negativity" for German Idealism. This "acting-out" has its own inescapable rationality: the immediacy of one's (emotional and conscious) survival in the "death struggle" of the Hegelian demand for recognition. Care and cure cannot be summed up as an accurate diagnosis and prescription. In my practice, this (not so) simple recognition of the other's freedom had a constant practical impact. One of society's responses is the development of a "third sector", non-profit organizations outside of organized social systems which answer its latencies such as individual and social complexity but whose precarious survival depends on their perceived immediate social utility.

4. Finally, let us try to be creative

At the end of this general survey, limiting their scope to the HCV epidemic, four options are possible.

- The first would keep the status quo, leaving the community with the belief that harm reduction is efficient, efficiency which could be boosted by additional funding of each of these actions and a better collaboration between services leading to integration in drug treatment programmes which would encompass them all. The sole aim of many papers published in journals dedicated to drug use and DUs is to convince their reader of its validity. This position is held by each subsystem which, to survive and even grow has to convince its environment of its performance. In my opinion, it may appear as the less costly in energy and financial involvement, but I believe, in the long term, it will be the less efficient.
- The second is more ambitious. It considers HCV hepatitis as an epidemic which should be controlled and DUs as users of services supplied by the healthcare system which may not be spontaneously desired by DUs but which use such as the treatment of HIV and hepatitis should be implemented to control these epidemics. From a DU's stand point HCV hepatitis cannot be considered alone. It is never more than a part of his "being-here" for which society's goals of harm reduction may not be relevant. To succeed society has to propose an environment "good-enough" to enable him to live without a continuous help of drugs. This option depends on the assumption that a better knowledge and a better management could control the HCV epidemic. Today, it remains a "wishful thinking" of existing social systems:
  - The initial assumption would be that the control of the HCV epidemic should associate prevention of new infections to the treatment of "all" (at least a large majority) the infected DUs (even not in DTP) to decrease viral prevalence to a level which would, by itself, limit the new contaminations, passing from an epidemic to sporadic cases, evolution observed for HIV in most countries where the initial prevalence remained low.
  - The first step would design and conduct an ethno-epidemiological study of a population in a geographical delimited area relevant for the proposed intervention. It would collect its socio-demographics, health status, social networks, drugs consumed and risks associated to that consumption, viral status and use of social and health care as well as its motivations, desires and plans (152).
  - From that collection, an analysis would define potentially different subgroups which would be targeted for different interventions which would try to build a "cultural" environment including a positive vision of HCV care and the conscience of the necessity of a global commitment needed to control the HCV epidemic. It would try to understand its course among these different subgroups including the possible viral reservoirs among DUs who do not attend healthcare services. The first goal of these programmes would be to win the trust of the concerned DUs by proposing services answering their need (desires). Beside proposing substitution treatments or social help to find work or housing, considering the cost of harm reduction and HCV treatment, one could propose conditional cash transfer or vouchers which have been used successfully in many countries to improve access to school or healthcare programmes and which is one of the few incentives proven to be efficient in cocaine addiction (153,154). Heroin treatment should be considered. It has been shown to be significantly more effective than methadone for difficult to maintain patients (155,156). This efficacy was also present in DUs without previous maintenance treatments (157). It can be delivered intranasally or orally (158). It has been shown to be cost-effective (159).

HCV prevention and treatment would only come second, tailored to the course of the epidemic, targeting opinion leaders through peers' interventions explaining the ethical goal of the project which would not be limited to the individual gain of the cure of one's hepatitis but would want to control the HCV epidemic in the area, control which would benefit not only DUs but also their family, friends and neighbors. Their success would be conditioned by a complete appropriateness between the discourse and the means: To improve the impact of NSP, a significant rise would be mandatory to decrease significantly the occurrence of receptive exchanges. It could mean a tenfold increase in the number of syringes exchanged, but it would not be enough. NSP should shift from exchange to distribution (160) allowing IDUs to store sterile syringes for future use and "providers" to distribute syringes to other IDUs who are in need of sterile syringes and cannot access a NSP or a pharmacy (161) This would help to cover unexpected "craving" episodes in former IDUs at times when pharmacies and NSP are closed which represent, at least in my experience, a significant cause of new contaminations. Home self-test for the diagnosis of HIV and HCV infection should be an option (65). As long as the HCV prevalence remains high, to be efficient, NSP as well as potential consumption rooms should be located in the neighborhood of every drug scene (162-164) embedded within existing spatial and social relations of DUs (165). Outreach, bringing services to the DUs with the lowest social functioning can also decrease NSS). Open scenes, where users could come to buy their drugs, find NSP and meet harm reduction services, could reduce the level of NSSHCV screening could only be considered if a treatment could be proposed to every infected DU. Interventions should be adapted to the evolution of each case. Building trust takes time, even more when every partner (from customers to professionals) are concerned.

- The simplistic idea that one would only need to bring potential actors together to carry out a community project is long overdue [166]. Understanding the implications of the affiliation of professionals to social sub-systems could help them as well as those responsible for leading and managing programs to consider the limits of their individual scope, the need for an evolution of their missions and for new cooperative programs. The evolution of the French care of DUs' hepatitis C bears witness of its feasibility. To reach these goals, time and specific resources must be allocated and a common will and trust between the different actors is mandatory to overcome the existing barriers to an effective integration of prevention and treatment of hepatitis C (167-169). The proposed approach makes the control of the HCV epidemic an example of a new health policy paradigm: efficient integrated services (medical and social) based on the knowledge of the health of a population in a designated area as advocated by most groups working on the improvement of clinical effectiveness. This multilevel approach to change should include the individual, group/team, organization, and larger environment/system level (170).

- The third alternative would be the legalization (not a simple depenalization) of drug consumption. Of course this proposal may appear heretic when one considers drug related deaths and comorbidities. However, the rational behind the "war on drugs" was its possible success. 40 year after its implementation, one is forced to observe its failure,

failure which has a precedent with alcohol prohibition in the United States (171-181). The belief that this legalization would result in a huge increase in drug consumption can be compared to the fantasy of an increase in sexual promiscuity induced by sexual education in the eighties, which was proven to be false. The obvious benefit would be the huge amount of taxes which escapes today every government. The drug market is still one of the most perfect examples of a free market economy adapting its products to its customers and one of the most profitable. Of course, it would mean a negative impact on many social sub-systems devoted to this war like justice, police, customs or, even, medicine with a significant reduction of state spending. They would not able to "understand" a proposal which would negate the mission which justifies their existence and reduce their "power". A global vision would be mandatory. One must also not forget drug dealers who have an interest in keeping their trade illegal and can spend large sums of money to bribe people who are able prevent that evolution. An initial transfer of marijuana market from organized crime to state management could assess the risks and benefits of this change of policy. Of course, its impact on the HCV epidemic would wait heroin and cocaine legalization which would only reduce the number of new contaminations.

- The fourth and last solution would be the development of a vaccine comparable to the HBV vaccine and which could be implemented on a population basis at least at adolescence. Of course this solution, when available, could improve each one of the previous solutions.

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