REVIEW ARTICLE
Evolution of HCV incidence in drug users in France

D. LUCIDARME[1,2,3]*, C. DUBURQUE[1,2,3], P. BULOIS[1,2,3] AND B. FILOCHE[1,2,3]

[1] *Université Nord de France, F-59000 Lille, France*
[2] *UCLille, F-59000 Lille, France*
[3] *Groupe Hospitalier de l'Institut Catholique Lillois/Faculté Libre de Médecine, F-59000 Lille, France, Service de Pathologie Digestive*

SUMMARY

Over the last 40 years, the dynamics of hepatitis C virus (HCV) infection in drug users has been affected by the illicit drug market, the health environment including the devastating impact of the HIV/AIDS epidemic which erupted in the 1980s, and the diffusion of substitution treatment beginning in 1995. The purpose of this literature review is to present the dynamics of HCV infection in drug users in France over the last 40 years. Two prevalence studies of HCV infection in the general population were conducted by the French Institute for Public Health Surveillance in 1994 and 2004 and were the touchstone data sources for this analysis. Hypotheses constructed from the findings of these two studies were examined in light of results reported by multicentre prevalence and incidence studies in drug-user populations. The incidence of HCV infection in drug users in France reached a peak in the late 1980s or early 1990s after a lengthy period of epidemic expansion. Implementation of a risk reduction policy enabled a very significant reduction in the incidence of HCV infection in drug users over the last 20 years, leading to incidence figures which are now 10–15% of the 1990 estimate.

Key words: Drug use, HCV, HIV, incidence, France.

INTRODUCTION

How many drug users are infected each year by the hepatitis C virus (HCV) in France? It is not easy to provide a reliable answer to this question. It is even more difficult to reconstitute the pattern of the epidemic since the dynamics of viral infection are affected not only by the illicit drug market, but also by the health environment, including the devastating impact of the HIV/AIDS epidemic which erupted early in the 1980s.The HIV/AIDS epidemic induced a change in drug-user behaviours, even before the institution of public policies. Until the early 1990s, the literature on the epidemiology of drug use in France was very limited.

Two periods can be distinguished: the first from 1970 to 1995 and the second from 1995 to the present time. The year 1995 can be seen as a turning point of the HCV epidemic among drug users since it was during that year that substitution treatment became widely available in France as did anti-HIV triple therapy, inflecting the course of the AIDS epidemic and HIV-HCV co-infection. Since 1995, in contrast with the earlier period, there has been a more abundant source of epidemiological data, most coming from the French drug abuse observatory (Observatoire français des drogues et toxicomanies; OFDT)

* Author for correspondence: D. Lucidarme, M.D., Service de Pathologie Digestive, Centre Hospitalier Saint Philibert, 115 rue du Grand But, 59462 Lomme Cedex, France.
(Email: lucidarme.damien@ghicl.net)

and the French Institute of Health Surveillance (Institut de veille sanitaire; InVS). The purpose of this literature review is to provide readers with the most factual presentation of the dynamics of the HCV epidemic in drug users in France over the last 40 years.

BACKGROUND

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) distinguishes experimentation, defined as use of an illicit drug at least once in one's life, from problem drug use, defined as 'injecting drug use or long duration/regular use of opioids, cocaine and/or amphetamines during the preceding years by persons in the 15–64 years age group' (EMCDDA, 2010; http://www.emcdda.europa.eu/stats09/pdu/methods).

The number of problem drug users in France in 2006 ranged from 210 000 to 250 000 persons, with about half concerning medically prescribed substitution treatments. Among problem drug users, about 145 000 would have used intravenous injection at least once in their lives [1].

Modalities of HCV transmission

Blood-borne infection is the main route of HCV transmission. This occurs when the blood of an infected person comes in direct contact with the blood of a non-infected person. Transmission between sexual partners is very low and favoured by HIV co-infection. Injecting drug use is currently the main source of infection in France. Needles and syringes have the greatest potential for HCV transmission because of their direct contact with blood during the injecting procedure. However, HCV-RNA has also been found in 25–40% of filters, cups and rinse-water samples [2]. An experimental study showed that HCV maintained outside the human organism in ambient air preserves its infective power for at least 16 h [3].

Sharing needles and drug paraphernalia between injectors is the dominant mode of transmission in injecting drug users. Unlike HIV transmission, sharing material used to prepare the injection, and in particular the filter, without sharing needles, is a source of HCV transmission between injecting drug users [4–6]. Of all subjects who had a seroconversion, the proportion which could be attributed to recipient and/or filter sharing was 13% [4]. In recent years, sniffing has been considered as a non-negligible risk

factor for HCV infection in subjects not using the intravenous route [7, 8].

About 75% of infected subjects remain chronic carriers and thus susceptible to transmitting the virus [9]. Furthermore, spontaneous or treatment-induced cure of hepatitis C does not lead to sustained immunity. HCV re-infections have been reported in recipients of numerous blood transfusions [10] and in drug users [11, 12]. Although the issue is controversial [13], patients who have eliminated the virus spontaneously apparently have a lower risk of developing chronic disease after a new infection than those who are HCV naive [14, 15].

Diagnosis of HCV infection

The diagnosis of HCV infection requires the demonstration of anti-HCV antibodies in the patient's serum. Despite the apparent simplicity of this diagnostic procedure, its implementation in epidemiological studies including drug users is a complex problem for at least three reasons.

First, drawing a venous blood sample is often difficult in drug users because of an altered venous network coupled with non-cooperation. This can bias epidemiological studies by excluding from screening a significant proportion of subjects at risk. Alternative methods such as screening via volunteer reports [16], or using saliva [5, 17] or capillary samples [18] have been applied in many studies to avoid this problem. However, the wide range of assay methods compromises comparisons of HCV prevalence reported in different studies.

Second, screening for HCV infection was not possible before the first-generation of anti-HCV antibodies became available in 1990. Consequently, the incidence before this date has to be reconstructed using mathematical models which take into account epidemiological data available at the time of the study and knowledge about the natural history of the disease.

Third, re-infection can be missed if the diagnosis of spontaneous cure is not established after the first infection [19].

Modalities for an epidemiological evaluation of HCV transmission

The fundamental knowledge which has emanated from epidemiological studies measuring prevalence, incidence and force of infection, particularly

regarding the specific aspects of the problem of HCV infection in drug users, should be underscored.

Prevalence counts all cases at a given moment. Prevalence varies when cure rate and deaths do not balance out disease incidence. A decrease in the prevalence of HIV infections in drug users during the 1990s paralleled a fall in the incidence of infection and a rise in AIDS-related deaths. Regarding drug use, initiation of new subjects to injecting practices or a positive migration balance of drug users can lead to an increase in their number. A fall in the number of drug users can result from discontinuation of drug use or injecting practices, or also from user death. In a retrospective cohort of 23 000 persons apprehended for heroin, cocaine or crack abuse in the period 1992–2001, the uncorrected death rate was 7·3 deaths/1000 person-years [20]. Inversely, if a disease is non-fatal, prevalence generally remains stable for decades even if the incidence has become low or even zero.

Incidence rate is used in epidemiology to describe the dynamics of a given disease in a given population. Variations in incidence in a sub-population do not necessarily reflect variations of incidence in the general population if the incidence in the sub-population is different from that in the general population. The methodological difficulty specific to the study of HCV infection in drug users results from the fact that the endemic situation of the sub-population of drug users has evolved over the last 40 years.

Incidence can be measured prospectively during the course of a longitudinal follow-up study of a cohort of drug users who were seronegative at inclusion. Setting up this type of study is rather difficult because a large number of subjects can be expected to be lost to follow-up at the end of the observation period. Moreover, different biases occur, especially concerning sample representativeness, and also concerning follow-up and adherence, potentially compromising results. Obtaining a representative sample is the most difficult element because the populations at greatest risk of viral infection are also the most difficult to include in epidemiological surveys because of their substance dependence and marginal social status.

Incidence can also be measured indirectly using retrospective studies by dividing the prevalence by the number of years since the first risk event, i.e. the first injection, and the date of the first serology test. This type of measure can be proposed only if the delay is short enough to correspond to a stable incidence over time. As a general rule, sub-populations of users aged <25 years and injectors for <2 years are distinguished in the literature. These two parameters define the category of 'new injectors' which can be used to evaluate the renewal of the injecting drug user population.

Force of infection is a measure of the risk of becoming infected, defined as the *per capita* rate at which susceptible individuals acquire infection [21]. Force of infection can be estimated from prevalence data as a function of time of exposure to risk. Regarding drug use, the time of exposure is defined as the time from the first injection to the moment of evaluation. The force of HCV infection in injecting drug users is not linear over time. It is very high during the first 2 or 3 years of injecting practices and decreases very rapidly thereafter. This decrease can be explained, at least in part, by changing risk practices, but especially by a saturation phenomenon: the higher the proportion of infected subjects, the lower the proportion of subjects susceptible to becoming infected. Thus, the concept of force of infection is in contradiction to the idea by which the difference observed between the patterns of the HCV and HIV epidemics would be related to the higher prevalence of HCV infection in drug users. It is the change to injecting drug use that is the key element in the HCV epidemic.

Methodology for the present analysis

Two prevalence studies on HCV infection in the general population conducted in France by the InVS in 1994 [22] and in 2004 [23] constituted the touchstone data sources for the present analysis. Despite the fact that general population studies can underestimate categories of statistically marginal subjects, the observations made during these two studies lead to hypotheses concerning the dynamics of HCV infection in drug users in France. This approach has the advantage of focusing on two large-scale and methodologically sound studies of representative populations.

The hypotheses constructed on the bases of the general population studies were then examined in light of the multicentre data available for drug-user populations concerning HCV prevalence [16, 18, 24, 25] and incidence [5] as well as modalization work [21, 26, 27].

Finally, single-centre studies [17, 28, 29] provided complementary insight for understanding the dynamics of HCV infection.

DYNAMICS OF THE HCV EPIDEMIC FROM 1970 TO 1995

The HCV and HIV epidemics among injecting drug users occurred as a result of massive heroin consumption, the predominant illicit drug in France for 25 years. Massive heroin consumption began in France in the early 1970s and concerned about 10 000 users [30]. During the second half of the 1970s, zones of use were mainly the outskirts of several large cities in southern France and the suburban areas of greater Paris. Use then spread to the Lyon region before becoming a general phenomenon in the 1980s covering the entire country, finally reaching the East then the North of France. Many routes of administration can be used for heroin. It can be ingested, inhaled, injected or smoked. In France, the persistence of intravenous injections from 1970 to 1995 was related, as in Europe and the USA, to the sole availability of an injectable form [31].

In the 1980s, no data were collected concerning HCV or HIV infection in drug users. One retro-calculation model of the HCV epidemic using data from a previous study [22] suggested a regular increase in incidence from 1970 to 1990 with a figure of about 15 000 non-transfusion-related incident cases for 1990, including 70% or about 10 000 ± 1000 suspected drug use-related cases [27].

HCV incidence probably reached a peak in the late 1980s or early 1990s in drug users because drug-use patterns beyond this period exhibited a double phenomenon of geographic and demographic saturation. After a long phase of expansion, the HCV epidemic finally involved the entire French territory, leading to a waning force of infection and a limited number of incident cases in new injectors in each region. A study conducted in Lille in 1991 illustrated the second saturation phenomenon: the annual incidence of HCV infection was 50% in first-year heroin injectors while 3 years after starting injections 90% of injectors were HCV-positive [29]. In this study, 57% of users had started drug injections <2 years earlier. The force of infection was consequently maximal during the first year producing an inevitable risk of infection. During this period, initiation to injecting practices was synonymous with HCV infection.

In 1993, it was estimated that there were at least 160 000 heroin addicts in France, with no information on the proportion of injectors or former injectors [32]. In a study conducted in 1994 in a sample of beneficiaries of the national health care insurance fund residing in four regions of France who volunteered for a health examination, the estimated prevalence of HCV infection was 1·05% [95% confidence interval (CI) 0·75–1·34]. Injecting drug use was the source of infection for 29% in the 20–59 years age group [22]. Extrapolating these data to the national census data of 1990 for the same age group and considering that the number of subjects aged <20 or >60 years with drug use-related HCV infection is marginal, the estimated number of HCV-positive drug users was 92 000 ± 14 000.

DYNAMICS OF THE HCV EPIDEMIC FROM 1995 TO 2010

Awareness of the catastrophic consequences of the HIV epidemic and the very high prevalence of HCV infection, and also the high rate of death by overdose, led to a new 'Risk reduction' policy financed by the French Ministry of Health which stipulated, among other measures, that dispensaries in France would make over-the-counter sterile injection kits (Stéribox®) continuously available, that the needle exchange programme would be developed, that care centre structures would be created with housing accommodation, and finally that full-scale availability of substitution treatments would begin in 1995. In 2007, the national health fund reimbursed around 96 000 persons for prescription high-dose buprenophine (HDB) and around 24 000 for prescription methadone [33].

Schematically, within a period of a few years, the environment changed significantly from one dominant substance (heroin) with one route of administration (intravenous injection) and one zone of consumption (urban areas) to a more complex situation characterized by widespread diffusion of cocaine and its derivatives, multiple-drug consumption, misuse of HDB, changing modes of consumption with a decline in injecting practices, and the emergence of different more festive areas of consumption [34, 35]. Thus, in this context of major mutations, and despite more abundant epidemiological data, the impact of the risk reduction policy on HCV transmission is difficult to ascertain.

Evolution of the number of HCV-positive drug users from 1994 to 2004

In 2004, the number of persons aged 18–80 years living in metropolitan France who were seropositive for anti-HCV antibodies and who had injected or

inhaled illicit drugs at least once in their life was estimated at about 105 000 (95% CI 40 000–154 000) including about 7700 ± 800 who had never injected (sniffers only) [36].

The Coquelicot multicentre survey conducted in 2004 among drug users (injectors or sniffers at least once in their life) took blood samples to measure the prevalence of viral infections: the HCV prevalence was 59·8% compared to 10·8% for HIV, giving a 5·54-fold difference [18]. In 2000, the number of HIV-positive subjects among drug users was evaluated at 20 200 (95% CI 14 300–29 100) [37]. If the 20 200 figure is multiplied by 5·54, the estimated number of HCV-positive drug users reaches 112 000 (95% CI 79 000–160 000). Despite the potential bias of this data source, it can be estimated that the number of HCV-positive drug users in 2004 ranged from 105 000 to 112 000.

The difference in the number of HCV-positive drug users estimated for 2004 (95% CI 105 000–112 000) and 1994 (92 000 ± 14 000) probably corresponds to the in-out balance (new infections minus deaths). The number of deaths in problem drug users can be extrapolated by multiplying the total drug-user population in 1999 (95% CI 142 000–176 000) [38], by the mortality rate of 7·3 deaths/1000 person-years [20], giving about 1000–1300 deaths annually. Considering that the prevalence of HCV infection in problem drug users was 60% [18], an estimated 600–800 HCV-positive drug users died annually from 1994 to 2004, or about 6000–8000 deaths for the decade considered. Consequently, the number of incident cases of hepatitis C in HCV-positive drug users between 1994 and 2004 would range from 5000 to 42 000 (taking into account the confidence interval), for an estimated average of 500–4200 new cases per year. An average of 500–4200 new cases of HCV infection per year in drug users from 1994 to 2004 does not mean that the incidence was stable during this period. Since the early 1990s, the trend has been towards a fall in HCV incidence. Consequently, the annual incidence of HCV in 1994 was probably in the neighbourhood of 4200 new cases per year while in 2004 it was closer to the lower figure than the higher one.

Evolution of the number of incident cases of HCV infection from 1999 to 2004

A longitudinal study of HCV infection in the drug-user population was conducted in the North and East of France from 1999 to 2001. The measured incidence was 9/100 person-years [5] and 11/100 person-years in active injectors, i.e. persons who had injected drugs at least once during the 6 months preceding inclusion. Extrapolation of these results to the number of presumed HCV-negative active drug users estimated at that period gave about 3500 (95% CI 2700–4400) new cases of infection in drug users in France annually [39]. This estimate would be valid for 1999 but not the entire decade since the incidence varied from one year to another.

The survey of HCV prevalence in 2004 [36] estimated that 7977 (95% CI 303–15 562) subjects aged 18–29 years were HCV-positive. Similarly, in the Coquelicot survey conducted in the same year [40], subjects born after 1974 and thus aged 18–29 years accounted for only 10·4% of the HCV-positive population, i.e. 11 648 (95% CI 8200–16 600) subjects considering the overall estimate of 112 000 (95% CI 79 000–160 000) persons established earlier from the same study. The range obtained from these two estimates, 7977–11 648, gives an estimate of the number of subjects infected by the virus from 1999 to 2004, accepting the hypothesis that the number of subjects born before 1975 and infected from 1999 to 2004 would be marginal.

Thus, considering that from 1999 to 2004 about 8000 to nearly 12 000 new HCV infections would have occurred, including 2700–4400 for 1999 alone, it can be reasonably estimated that about 1000 (95% CI 500–2000) drug use-related infections occurred in 2004. This very significant decline in HCV incidence in drug users could be nonlinear from 1994 to 2004, with a more marked fall starting in 2000 after the risk reduction policy reached maximum coverage [41] and is illustrated by the very clear fall in HCV prevalence in the general population for the 20–29 years age group from 1994 to 2004 [42].

Evolution of HCV incidence from 2004 to 2010

There was no direct measurement of HCV incidence in drug users in France from 2004 to 2010. However, several indirect evaluations of incidence in new injectors were made using prevalence data from injectors aged <30 years or <25 years, depending on the study. Several surveys conducted in users attending care centres, general medicine clinics [18, 25, 28] or first-line structures (Centre d'accueil et d'accompagnement à la réduction des risques pour usages de drogues; CAARUD) [43] appear to indicate that the decline in HCV incidence continued.

The HCV prevalence in drug users aged <30 years was 44% in the first Coquelicot study in 2002 in Marseille [44], 29% in the second study in 2004 in five French large cities [18], and only 7% in 2007 in the microstructure medical network in Alsace [28]. The data from these studies must, however, be interpreted with caution because of the wide geographic and methodological differences of the data sources.

The prevalence figures for positive HCV serology reported by injecting drug users aged <25 years attending care centres with housing accommodation in 1998 [16] and first-line structures in 2006 [43] were 40·8% and 12·2%, respectively. In an exhaustive survey conducted during the same week in 2006 and in 2008, users aged <25 years attending first-line structures (CAARUD) who had already used the intravenous route reported serology results showing a decline in HCV prevalence from 22·5% to 14·3% [43].

Thus the incidence of HCV infection in drug users appears to have declined very significantly over the last 20 years to the point where the current estimates are 10–15% of those established for 1990. However, to this estimate must be added HCV-positive subjects issuing from migrant populations, often from Eastern Europe or Caucasia, whose number is extremely difficult to determine due to the lack of available data.

These findings are quite similar to those reported for a cohort of drug users in Amsterdam where the HCV incidence would have fallen from 27·5% around the end of the 1980s to 2% in 2005 [45]. In The Netherlands, a policy of risk reduction had been established early in the 1980s.

HYPOTHESES CONCERNING THE DECLINE IN HCV INCIDENCE

Decline in use of intravenous injections

The decline in needle sharing may not have been sufficient to alter the course of the epidemic because unlike HIV, HCV can also be transmitted via the material used to prepare the injection. A change in habits in favour of the inhalation route with lesser use of the intravenous route in new users could have been a determining factor. As early as 2003, the TREND system had data to put forward the hypothesis of a decrease in the proportion of injecting users among problem users, particularly heroin addicts [46]. For cocaine, injection is the second most common route of

administration, after sniffing, illustrating the fact that the younger generation has preferred, as it has for heroin, inhalation over intravenous injection. Similarly, in users attending first-line structures (CAARUD) the proportion having never used intravenous injection has tended to increase [43]. It can also be noted that injection in a festive environment remains a marginal phenomenon.

The lesser use of the injection route of administration in new users might correspond to later initiation to injection practices in the course of drug use. Evidence from most of the epidemiological studies does not appear to be in favour of this hypothesis since the median age at first injection would be around 20 years [18, 29].

One consequence of lesser use of the intravenous route is a limited renewal of the user population in drug users attending care centres where there has been a very clear decline in the proportion of new injectors. In 1993 and 1998, the proportions of injectors aged <25 years attending care centres with housing accommodation (CSST/CSAPA) were respectively 24% and 16% [16]. In the Coquelicot study of 2004, 8% of subjects had injected or sniffed at least once and only 3% of injectors were aged <25 years [40, 47]. This phenomenon is not limited to France. In Switzerland, the proportion of drug users who began injecting <2 years before the study fell from 18·7% in 1993 to 3·3% in 2006. An older attending population, with a mean age of 26 years in 1993 and 36 years in 2006, was a consequence of this phenomenon [48]. This limited renewal of the drug-user population attending care centres explains a large part of the stability over time of the HCV prevalence in most cross-sectional studies conducted from 1991 to 2004: 50–80% [17, 18, 24, 29, 49].

Although the risk of infection is lower for inhalation than for intravenous injection, the proportion of new drug users contaminated by the nasal route appears to be increasing, becoming perceptible [50].

Decreased force of infection

In intravenous injectors, the second factor would be a decrease in the force of infection with later consequences and less massive HCV infection than in the early 1990s, even if the first years of drug use by intravenous injection remains a high risk period for HCV infection. This phenomenon would result from less frequent injections and better compliance with the

rules of asepsis. In 2008, only 20% of users attending first-line structures (CAARUD) who had consumed heroin within the preceding month had consumed daily [33]. Thus the common habit of several injections per day before the advent of substitution treatment was less common, leading to an inevitable drop in injection frequency and thus in the associated risks.

In an incidence study on HCV infection conducted in the North and East of France in 1999, the annual HCV incidence was 17·5% in drug users of <2 years and 6% in users of >2 years [5]. In the 2004 Coquelicot study, the force of infection remained high. Despite a smaller number of subjects concerned, the HCV prevalence in drug injectors aged <25 years was 32·1% [47]. Thus in recent years the cumulative incidence of HCV infection after 5 years of injecting practices would be to the order of 40–50% compared with 90% in the early 1990s [29].

Better access to hepatitis C treatment for drug users

France is the European country which has done the most to provide care for hepatitis C patients [51]. At the end of 2005, an antiviral treatment had been delivered for 16% of the prevalent cases of HCV infection. This diffusion of treatment would be the source of a considerable decline in the proportion of HCV-seropositive subjects with viraemia which was 81% in 1994 [22] and 57% in 2004 in the 20–60 years age group [42]. In drug users, treatment cannot be dissociated from prevention and screening for new infection. Access to treatment has also been the object of much attention. In 2008, 70·5% of drug users attending first-line structures (CAARUD) who were HCV-positive consulted a doctor for this condition and more than one-quarter (28%) were taking treatment, i.e. 5·5 percentage points above the level observed in 2006 [46]. The treatment of drug users is favoured by the presence of a favourable genotype observed in about half of the cases. The results obtained in terms of response to treatment, adverse effects, and premature discontinuation of treatment are globally comparable to those observed in non-drug-user patients [52, 53]. In this context, multidisciplinary management of addiction-related problems, hepatitis C, and frequently associated psychiatric comorbidity is crucial [54]. The proportion of re-infections after treatment to cure is not >10% [55–57] so that there is no reason to proscribe treatment in drug users.

CONCLUSION

HCV infection in drug users in France apparently reached a peak early in the 1990s after a long phase of expansion of the epidemic. Up to that period, HCV infection was almost inevitable for injecting drug users after a few years of practice. The policy of risk reduction progressively modified this situation, even though the consequences in terms of HCV infection remained uncertain for a lengthy period. Considering the data currently available, the paradigm according to which this policy would have a limited impact on HCV infection [18] should be revisited. The main success of this policy would be first and foremost to have contributed to a reduction in the number of injectors and to favour alternative modalities such as inhalation and smoking, but also to have led users to avoid risk-taking when injecting and to discontinue this mode of administration or limit its frequency. Better access to antiviral treatment for drug users may also have contributed to these results. These findings provide an incentive for continuing prevention and screening measures against new infection within the framework of a risk reduction policy.

DECLARATION OF INTEREST

None.

REFERENCES

1. **Costes JM.** The prevalence of problem drug use in France: estimates for 2006 (http://www.ofdt.fr/ofdtdev/live/english-tab/engpubli/tends/tend69eng.html). Accessed 2009.
2. **Crofts N, et al.** Minimising harm from hepatitis C virus needs better strategies. *British Medical Journal* 2000; **321**: 899.
3. **Kamili S, et al.** Infectivity of hepatitis C virus in plasma after drying and storing at room temperature. *Infection Control and Hospital Epidemiology* 2007; **28**: 519–524.
4. **Hagan H, et al.** Sharing of drug preparation equipment as a risk factor for hepatitis C. *American Journal of Public Health* 2001; **91**: 42–46.
5. **Lucidarme D, et al.** Incidence and risk factors of HCV and HIV infections in a cohort of intravenous drug users in the North and East of France. *Epidemiology and Infection* 2004; **132**: 699–708.
6. **De P, et al.** Risk of hepatitis C virus transmission through drug preparation equipment: a systematic and methodological review. *Journal of Viral Hepatitis* 2008; **15**: 279–292.

7. **Tortu S, et al.** Sharing of noninjection drug-use implements as a risk factor for hepatitis C. *Substance Use and Misuse* 2004; **39**: 211–224.

8. **Martinez A, Talal AH.** Noninjection drug use: an under-appreciated risk factor for hepatitis C virus transmission. *Liver International* 2008; **28**: 757–760.

9. **Micallef JM, Kaldor JM, Dore GJ.** Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. *Journal of Viral Hepatitis* 2006; **13**: 34–41.

10. **Lai ME, et al.** Hepatitis C virus in multiple episodes of acute hepatitis in polytransfused thalassaemic children. *Lancet* 1994; **343**: 388–390.

11. **Bowden S, et al.** Detection of multiple hepatitis C virus genotypes in a cohort of injecting drug users. *Journal of Viral Hepatitis* 2005; **12**: 322–324.

12. **Micallef JM, et al.** High incidence of hepatitis C virus reinfection within a cohort of injecting drug users. *Journal of Viral Hepatitis* 2007; **14**: 413–418.

13. **Van De Laar TJ, et al.** Frequent HCV reinfection and superinjection in a cohort of injecting drug users in Amsterdam. *Journal of Hepatology* 2009; **51**: 667–674.

14. **Grebely J, et al.** Hepatitis C virus reinfection in injection drug users. *Hepatology* 2006; **44**: 1139–1145.

15. **Osburn WO, et al.** Spontaneous control of primary hepatitis C virus infection and immunity against persistent reinfection. *Gastroenterology* 2010; **138**: 315–324.

16. **Six C, Hamers F, Brunet JB.** HIV, HCV and HBV infections among drug users attending care centres with housing accommodations 1993–1998. *Bulletin Epidémiologique Hebdomadaire* 1999; **32**: 1–4.

17. **Bello PY, et al.** Assessment of a hepatitis C virus antibody assay in saliva for epidemiological studies. *European Journal of Clinical Microbiology and Infectious Diseases* 1998; **17**: 570–572.

18. **Jauffret-Roustide M, et al.** A national cross-sectional study among drug-users in France: epidemiology of HCV and highlight on practical and statistical aspects of the design. *BMC Infectious Diseases* 2009; **9**: 113.

19. **Amin J, et al.** Potential biases in estimates of hepatitis C RNA clearance in newly acquired hepatitis C infection among a cohort of injecting drug users. *Epidemiology and Infection* 2007; **135**: 144–150.

20. **Lopez D, Martineau H, Palle C.** Mortality of individuals arrested for heroin, cocaine or crack use (http://www.ofdt.fr/BDD/publications/docs/eftadlk5.pdf). Accessed 2004.

21. **Mathei C, et al.** Evidence for a substantial role of sharing of injecting paraphernalia other than syringes/needles to the spread of hepatitis C among injecting drug users. *Journal of Viral Hepatitis* 2006; **13**: 560–570.

22. **Dubois F, et al.** Hepatitis C in a French population-based survey, 1994: seroprevalence, frequency of viremia, genotype distribution, and risk factors. *Hepatology* 1997; **25**: 1490–1496.

23. **Meffre C, et al.** Prevalence of hepatitis B and hepatitis C virus infections in France in 2004: social factors are important predictors after adjusting for known risk factors. *Journal of Medical Virology* 2010; **82**: 546–555.

24. **Valenciano M, Emmanuelli J, Lert F.** Unsafe injecting practices among attendees of syringe exchange programmes in France. *Addiction* 2001; **96**: 597–606.

25. **Palle C, Vaissade L.** The initial national results of the RECAP survey (http://www.ofdt.fr/ofdtdev/live/english-tab/engpubli/tends/tend54eng.html). Accessed 2007.

26. **Downs AM, et al.** Reconstruction and prediction of the HIV/AIDS epidemic among adults in the European Union and in the low prevalence countries of central and eastern Europe. *AIDS* 1997; **11**: 649–662.

27. **Deuffic S, et al.** Modeling the hepatitis C virus epidemic in France. *Hepatology* 1999; **29**: 1596–1601.

28. **Di Nino F, et al.** Screening and treatment of hepatitis C by the microstructure medical network in Alsace, France, 2006–2007. *Bulletin Epidémiologique Hebdomadaire* 2009; **37**: 4–8.

29. **Lucidarme D, et al.** Prevalence of hepatitis C, B and D markers and histopathological aspects in a group of intravenous drug addicts. *Gastroentérologie Clinique et Biologique* 1994; **18**: 964–968.

30. **Chossegros P.** Management of drug addiction in France (a short history). *Gastroentérologie Clinique et Biologique* 2007; **31**: S44–50.

31. **Toufik A.** Distribution of intravenous injection in France (http://www.ofdt.fr/BDD/publications/docs/tend5gb.pdf). Accessed 1999.

32. **Costes JM.** A prevalence estimate. In: Carpentier C, Costes JM, eds. *Drogues et Toxicomanies: Indicateurs et Tendances*, 1995, pp. 44–45.

33. **Toufik A, Escots S, Cadet-Tairou A.** Change in drugs use linked to the diffusion of substitution treatments. Illicit drug uses in France since 1999, from the TREND system. French Observatory for Drugs and Drug Addiction (OFDT), 2010.

34. **OFDT.** Drugs and drug use in France. Levels of use and recent trends 2007–2009. French Observatory for Drugs and Drug Addiction, 2010 Report (http://www.ofdt.fr/ofdtdev/live/publi/rapports/rap10/epfxacq1.html). Accessed 2010.

35. **OFDT.** Illicit drug use in France since 1999, from the TREND system. Costes JM (Dir.). French Observatory for Drugs and Drug Addiction, 2010, 191 pp.

36. **Meffre C, et al.** Prevalence of hepatitis B and C in France in 2004. Institut de veille sanitaire, Saint-Maurice, March 2007, 114 pp.

37. **Desenclos JC, Costagliola D, Commenges D, et al.** Prevalence of HIV infection in France. *Bulletin Epidémiologique Hebdomadaire* 2005; **11**: 41–44.

38. **OFDT.** Drugs and dependence: indicators and trends of the French Drug Abuse Observatory, 1999. French Observatory for Drugs and Drug Addiction.

39. **Emmanuelli J, Jauffret-Roustide M, Barin F.** Epidemiology of HCV infection among drug users, France, 1993–2002. *Bulletin Epidémiologique Hebdomadaire* 2003; **16–17**: 13–15.

40. **Jauffret-Roustide M, et al.** Estimate of HIV and HCV prevalence and patterns of drug users in France,

InVS-ANRS Coquelicot study, 2004. *Bulletin Epidémiologique Hebdomadaire* 2006; **33**: 244–247.

41. **Emmanuelli J, Desenclos JC.** Harm reduction interventions, behaviours and associated health outcomes in France, 1996–2003. *Addiction* 2005; **100**: 1690–1700.

42. **Delarocque-Astagneau E, et al.** The hepatitis C surveillance system committee and the scientific committee for the national prevalence survey of hepatitis B and C markers. The impact of the prevention programme of hepatitis C over more than a decade: the French experience. *Journal of Viral Hepatitis* 2010; **17**: 435–443.

43. **Cadet-Tairou A, et al.** Health status of drug users. Drugs and drug use in France. Levels of use and recent trends 2007–2009. Ninth Edition of the National Report of the TREND system. French Observatory for Drugs and Drug Addiction (OFDT), 2010.

44. **Jauffret-Roustide M, et al.** Impact of a harm-reduction policy on HIV and hepatitis C virus transmission among drug users: recent French data-the ANRS-Coquelicot Study. *Substance Use and Misuse* 2006; **41**: 1603–1621.

45. **Van Den Berg CH, et al.** Major decline of hepatitis C virus incidence rate over two decades in a cohort of drug users. *European Journal of Epidemiology* 2007; **22**: 183–193.

46. **Bello PY, Cadet-Tairou A, Halfen S.** Health status of problem drug users. Drugs and drug use in France. Illicit drug uses in France since 1999 from the TREND system. French Observatory for Drugs and Drug Addiction (OFDT), 2010.

47. **DREES.** Health status of the population in France. 2007 Report (http://www.sante.gouv.fr/IMG/pdf/esp2007-obj-56.pdf). Accessed 2007.

48. **Dubois-Arber F, et al.** Trends in drug consumption and risk of transmission of HIV and hepatitis C virus among injecting drug users in Switzerland, 1993–2006. *Eurosurveillance* 2008; **13**: 18881.

49. **Schmitt C, Bertel J, Jacob C.** Incidence of serological markers of hepatitis B and C viruses and HIV in a population of drug abusers hospitalized from 1990 to 1992. *Annales de Médecine Interne* 1994; **145**: 7–12.

50. **Aaron S, et al.** Intranasal transmission of hepatitis C virus: virological and clinical evidence. *Clinical Infectious Diseases* 2008; **47**: 931–934.

51. **Lettmeier B, et al.** Market uptake of new antiviral drugs for the treatment of hepatitis C. *Journal of Hepatology* 2008; **49**: 528–536.

52. **Bruggmann P, et al.** Active intravenous drug use during chronic hepatitis C therapy does not reduce sustained virological response rates in adherent patients. *Journal of Viral Hepatitis* 2008; **15**: 747–752.

53. **Chossegros P, et al.** A French prospective observational study of the treatment of chronic hepatitis C in drug abusers. *Gastroentérologie Clinique et Biologique* 2008; **32**: 850–857.

54. **Moussalli J, et al.** Management of hepatitis C among drug user patients. *Gastroentérologie Clinique et Biologique* 2007; **31**: 4S51–4S55.

55. **Backmund M, et al.** Treatment of hepatitis C infection in drug users. *Hepatology* 2001; **34**: 188–193.

56. **Sylvestre DL.** Treating hepatitis C in methadone maintenance patients: an interim analysis. *Drug and Alcohol Dependence* 2002; **67**: 117–123.

57. **Dalgard O, et al.** Treatment of chronic hepatitis C in injecting drug users: 5 years' follow-up. *European Addiction Research* 2002; **8**: 45–49.