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Hepatitis C virus reinfection among prisoners with sustained virological response after treatment for chronic hepatitis C

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Background & Aims: We estimated HCV reinfection rate and its associated risk factors in inmates with chronic hepatitis C who had achieved sustained virological response (SVR) after completing combination therapy while in prison.

Methods: Individuals who had achieved an SVR after treatment provided from January 2003 to December 2009 at four prisons in Catalonia, had been tested annually for HCV RNA and were in prison during 2010, were invited to complete a questionnaire regarding risk factors for reinfection. Incidence rate was calculated as 100 person-years of follow-up. Risk factors potentially associated with reinfection were evaluated by bivariate log-rank test and multivariate Cox regression analysis.

Results: One hundred and nineteen subjects who had achieved an SVR agreed to participate. 98% were male, with a median age of 33.3 ± 6.3 years and 81% had a history of injection drug use (IDU). After a mean follow-up of 1.4 years, HCV reinfection was identified in nine former IDUs, seven with HCV genotype switch, for an overall reinfection rate of 5.27 cases per 100 person-years. Reinfection incidence was significantly higher among active drug users (HR = 12.47; 95% CI: 2.90–53.71), HIV co-infected (HR = 9.95; 95% CI: 1.73–57.34), and those engaging in more than one risk behaviors after treatment (HR = 7.47; 95% CI: 1.19–46.89).

Conclusions: HCV reinfection among inmates after successful treatment is high especially in those with ongoing IDU. Preventative interventions at diagnosis and during and after HCV treatment should be strongly reinforced.

Keywords: Prisons; Chronic hepatitis C; RNA virus infection; Incidence; Risk behaviors.

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Abbreviations: HCV, hepatitis C virus; CHC, chronic hepatitis C; SVR, sustained virologic response; py, person-years; HR, hazard ratio; CI, confidence intervals; IDU, intravenous drug use; SD, standard deviation.

Introduction

Injecting drug use (IDU) has become the main transmission mechanism of HCV in most developed countries [1,2] and is the main contributor to both prevalent and incident HCV infections among prison inmates [3–6]. The WHO has officially endorsed the consideration of IDUs as a key group requiring targeted actions for viral hepatitis prevention and treatment [7], both of which shown to be cost-effective [8–10].

Incarceration has often been considered a barrier to chronic hepatitis C treatment [11,12], because of social and educational concerns and a higher risk of HCV reinfection [13–15]. On the other hand, incarceration offers a unique opportunity to identify previously undiagnosed HCV infections [16], and provide treatment for both HCV and drug dependence [17]. Indeed, several studies have shown that SVR rates in prisoners are equivalent to those achieved in the non-prison setting [18–20] and that treatment of this population is also cost-effective [20,21].

Nonetheless, the risk of reinfection after treatment is real and might jeopardize future cost-effective analyses (especially with the new directly acting antivirals) frustrating efforts to increase treatment uptake and access to more effective treatment strategies. Indeed, among IDUs, reinfection has been reported after successful treatment of acute and chronic HCV infection provided both in the community [22–24] and in the prison setting [25].

Close to 11,000 individuals are incarcerated at the ten Catalan prisons (Spain). The current prevalence of HCV infection in this population is close to 25% (most cases acquired through IDU), similar to that recently reported in 18 Spanish prisons [26] and 10 to 15-fold higher than estimates for the general population of Spain (1.6–2.6%) [27]. In the Catalan Penitentiary System, inmates with a history of IDU are routinely offered counseling and enrollment in the low-threshold methadone maintenance treatment (MMT) program. Directly supervised treatment is

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started during incarceration and, upon release, subjects are referred to a program's community-based facility. Post release follow-up, may vary depending on individual evaluation but includes daily methadone provision and weekly face-to-face interviews and urine drug screening, with take-home privileges granted when urine tests are repeatedly negative [28]. Chronic hepatitis C treatment is offered according to standard guidelines officially endorsed by the penitentiary healthcare system [29], after individual approval by the Catalan Advisory Council for Viral Hepatitis Treatment. For inmates who are unlikely to be incarcerated for the entire planned duration of therapy, treatment is deferred and they are adequately counseled and referred to specialized health-care units at tertiary hospitals after release to freedom. To prevent treatment interruption when release from prison comes unexpectedly, a network of collaborating community hospitals are readily accessible to complete treatment and follow-up. Between 2003 and 2009, over 600 inmates (more than 70% IDU and 25% HIV-co-infected) have been treated, with 62% achieving an SVR. However, no information is available on durability of the response.

Therefore, the objective of this study was to estimate the incidence rate and predictive factors of HCV reinfection following SVR in a large cohort of inmates who had received therapy during a seven-year period.

Patients and methods

Study population

This multicenter study included inmates who were treated for chronic hepatitis C as part of routine clinical practice at four prisons in Catalonia, between January 2003 and December 2009, and who met the following inclusion criteria: (a) having achieved an SVR (undetectable HCV RNA in two consecutive samples, six months after end of treatment); (b) being incarcerated during the first semester of 2010, and (c) accepting to be interviewed regarding pre-defined variables potentially associated with reinfection.

All patients had been treated, following standard recommendations, with weekly pegylated interferon α2b (1.5 μg/kg) or α2a (180 μg) plus daily weight-adjusted or fixed 800 mg ribavirin doses for 24 or 48 weeks (according to genotype), and anti-retroviral therapy in those co-infected with HIV. Sustained virological response was defined as a qualitative HCV RNA <50 IU/ml (Cobas Amplicor HCV Test v2.0, Roche Diagnostic Systems, Barcelona, Spain) 24 weeks after end of treatment.

Following SVR, patients were seen every 12 months, questioned about IDU relapse and retention in MMT and tested for HCV RNA. In those found positive, an additional sample was tested for viral load and HCV genotyping. In all samples (before and after treatment), HCV genotype was determined with a commercial reverse hybridization assay (InnoLipa HCV 2.0, Innogenetics, Ghent, Belgium).

The study was approved by the Justice Department of the Catalan Government. Eligible inmates were given written information about the study content and objectives and asked to sign the informed consent to participate. All subjects were specifically reminded that, as stated in the form, they would not receive any monetary compensation or penitentiary benefits for their participation, and that their responses would have no impact on their healthcare rights nor on their status within the prison.

Electronic clinical records from participating inmates were reviewed and the following data were retrieved: age, sex, country of origin (Spanish *vs.* foreign born), prior and current IDU, any recognized parenteral risk factor, HIV status, baseline viral load and HCV genotype, dates and duration of HCV treatment and outcome. Reinfection date was defined as the midpoint between the last negative and first positive HCV RNA test dates. Evaluation for this study was closed on June 30th 2010, at which time patients were finally categorized according to the primary end point (reinfection *vs.* no reinfection).

Interview

During a direct interview with the hepatitis C control program staff, a questionnaire (Supplementary data) was administered to all participating subjects regarding a set of variables potentially associated with reinfection, which were determined *a priori* and included IDU, engaging in risky sexual practices (sex with IDU partner, or $\geqslant 3$ different sexual partners per trimester) and tattooing performed during or after treatment. Details on the use of MMT during and after therapy were also recorded.

Statistical analyses

Reinfection incidence rate was calculated for the entire population and for subgroups, according to categorical variables (age, sex, country of origin, HIV status, methadone treatment, and the set of pre-defined risk factors) as cases per 100 person-year of follow-up after censoring at the last negative HCV RNA testing or at the midpoint between the last negative and first positive HCV RNA test dates for those with reinfection. Descriptive data were expressed as absolute numbers and percentages, average with standard deviation (SD). Reinfection curves were estimated using the Kaplan–Meier method and different groups of interest were compared using the log rank test. Bivariate and multivariate analyses were performed using Cox's proportional hazards model. Epidemiologically relevant variables potentially associated with reinfection (p value <0.10), were included in multivariate analysis using a backward stepwise approach, sequentially eliminated and subject to a likelihood ratio test. Crude and adjusted Hazard Ratios (HR) and their 95% confidence intervals were calculated. Two-sided p values <0.05 were considered statistically significant. All analyses were performed using SPSS version 18.0 statistical package (SPSS Inc., Chicago, IL, USA).

Results

Of 122 eligible patients, three (2.4%) were not enrolled (two refused to participate and one was released to freedom before being interviewed). Of the 119 subjects finally included (Table 1), the majority were men (97%), young (mean age 33.3 ± 6.3 years), Spanish born (96%), HIV negative (85%), and had a prior history of IDU (81%). Forty-seven of the 96 IDU (40%) had been on MMT for the entire duration of the study period (from treatment onset to evaluation in 2010). All patients were on low-threshold MMT program, started in prison and retained in community-based facilities. Methadone (mean daily dose was 80 mg) was provided daily and taken under supervision, unless granted take-home privileges, with periodical or random urine drug screening. One patient who had requested volunteer treatment withdrawal after SVR had methadone-dose tapering during follow-up and was taking a low dose at inclusion. Patients were followed for a total of 170.5 years (maximum of 1630 days; average 1.4 ± 0.3 years).

Regarding risk factors for reinfection, 12 (10.1%) admitted to IDU, 10 (8.4%) had tattooing, and 7 (5.9%) had risky sexual relations. Twenty-four (20%) subjects engaged in at least one risk-taking behavior and five (4.2%) admitted two or more risk practices.

Nine of the 119 subjects (7.6%) had HCV reinfection. In all but one patient, active viral replication was confirmed in a repeat sample. As summarized in Table 2, seven cases (78%) had reinfection with a different HCV genotype, one had no genotype switch (subtype of the pre-treatment isolate was unknown and no sample was available for parallel testing), and one was released from prison before a repeat sample could be obtained for HCV typing. Reinfection occurred in prison in one subject who remained incarcerated during the entire follow-up, while in the remainder (88.9%), who had been granted leave of absence or released after treatment, whether reinfection occurred within or outside prison could not be established. Among subjects with reinfection, the average follow-up since SVR was 1.72 years (maximum 1223 days), as compared to 1.4 years (maximum 1630 days) in those without reinfection ($p = 0.31$). All reinfections occurred in men with a prior history of IDU.

Table 1. Demographic and behavioural characteristics of patients with and without HCV reinfection after treatment-induced SVR.

Variable	Total n = 119 (%)	Reinfection n = 9 (%)	No reinfection n = 110 (%)	*p* value
Age (mean yr)	33.3 ± 6.3	29.9 ± 4.6	33.6 ± 6.3	0.051
Male sex; N (%)	116 (97.5)	9 (100)	107 (97.3)	0.79
Spanish-born	114 (95.8)	8 (88.9)	106 (96.4)	0.33
HIV infected	18 (15.1)	3 (33.3)	15 (13.6)	0.13
History of IDU ever	96 (80.7)	9 (100)	87 (79.1)	0.13
IDU during or after treatment	12 (10.1)	5 (55.6)	7 (6.4)	<0.001
Tattooing during or after treatment	10 (8.4)	1 (11.1)	9 (8.2)	0.55
Currently on MMT	47 (39.5)	1 (11.1)	46 (41.8)	0.06
High-risk sexual practices	7 (5.9)	2 (22.2)	5 (4.5)	0.08
No risk factor for reinfection	95 (79.8)	4 (44.4)	91 (82.7)	0.01
Any risk factor for reinfection	24 (20.2)	5 (55.6)	19 (17.3)	0.01
More than one risk factor	5 (4.2)	2 (22.2)	3 (2.7)	0.04

MMT, Methadone maintenance treatment.

Table 2. Characteristics of patients with HCV reinfection.

Case number	Age	Sex	Prior IDU	HIV infection	MMT	No. of risk factors	Days to reinfection	HCV RNA (IU/ml)*	HCV genotype before treatment	HCV genotype at reinfection
1	27	M	Yes	Yes	No	0	378	1.3×10^6	3	1
2	27	M	Yes	No	Yes	1	160	4.4×10^5	1	3
3	32	M	Yes	No	No	0	1095	7.5×10^5	2	1
4	36	M	Yes	No	No	0	1223	1.8×10^6	1	3
5	24	M	Yes	No	No	2	588	5.3×10^5	2	1
6	29	M	Yes	No	No	3	267	2.9×10^5	1	1$^{\Psi}$
7	28	M	Yes	Yes	No	1	332	1.2×10^6	1	3
8	38	M	Yes	No	No	1	716	1.1×10^3	1	3
9	28	M	Yes	Yes	No	0	892	2.3×10^6	2	Unknown**

IDU, injecting drug use; MMT, methadone maintenance treatment.
*Viral load at reinfection.
$^{\Psi}$HCV-1 subtype not determined.
**No sample available for retesting and typing. Patient released from prison before evaluation could be completed.

The overall incidence rate of reinfection was 5.27 cases per 100 person-years, for a projected cumulative reinfection incidence of 40.7% at 3.5 years following SVR (Fig. 1). Reinfection rate was three-fold higher among HIV co-infected than in HIV-negative subjects (13.41 *vs.* 4.04 per 100 person-years, respectively; $p = 0.01$), 13-fold higher among those reporting active IDU than in those never injecting or not relapsing after treatment (33 *vs.* 2.57 per 100 person-year, respectively; $p < 0.001$) and eight-fold higher in those engaging in more than one risk behavior than in those with only one or no risk behavior (37.01 *vs.* 4.24 per 100 person-year, respectively; $p < 0.001$). No significant differences in reinfection incidence rate were found with regard to tattooing (7.19 *vs.* 5.11 per 100 person-year, respectively; $p = 0.57$) nor with engaging in risky sexual practices (18.5 *vs.* 4.37 per 100 person-years, respectively; $p = 0.14$). Similarly, in former IDUs, no significant association was found between reinfection and being under MMT (1.64 *vs.* 7.49 per 100 person-years, respectively; $p = 0.25$). The only subject reinfected while still on MMT was the one leaving the program and receiving a low dose (10 mg) at the estimated time of reinfection.

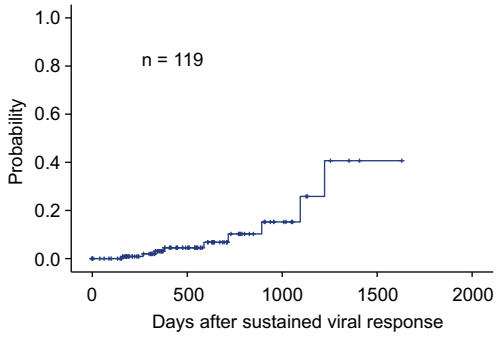

Fig. 1. Probability of HCV reinfection 3.5 years after treatment-induced SVR for the entire cohort.

Fig. 2 illustrates calculated reinfection incidences among patients subgrouped according to risk factors. It should be noted that reinfection rates were very high among subjects with active IDU and in those admitting to more than one risk behavior during or after treatment. In contrast, former IDUs who denied injecting

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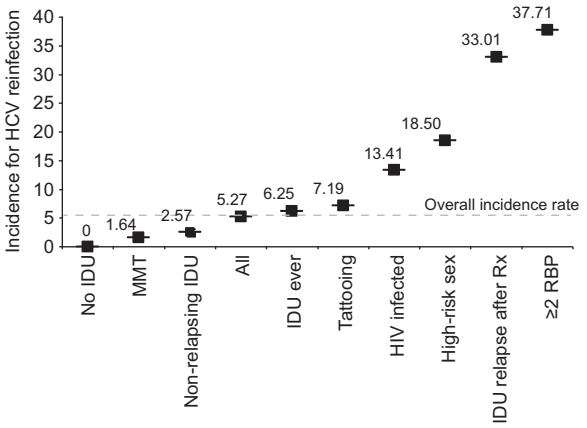

Fig. 2. Incidence by categories and risk factors for HCV reinfection after treatment-induced SVR.

drug use after SVR, and especially those under MMT, had reinfection rates below the estimate for the entire cohort.

As shown in Table 3, the three variables significantly associated with reinfection in bivariate analysis (HIV co-infection, injecting drug use during or after treatment, and engaging in two or more risk practices) were independently associated with HCV reinfection on multivariate analysis.

Discussion

Available data on the incidence of HCV reinfection among prisoners achieving an SVR after anti-HCV therapy is scarce. In a recent retrospective investigation among 53 inmates who had achieved an SVR after treatment, Bate *et al.* [25] identified nine cases of reinfection (17%) after a mean follow-up of 1243 days. Lower reinfection rates (0.8–3.2 per 100 person-years) have been reported among community-treated IDUs [23,30,31].

In the present study, the estimated reinfection rate for the entire cohort was 5.27 cases per 100 person-years, similar to those reported in high-risk community or incarcerated IDUs [23,25]. Projecting cumulative reinfection incidence over time from this estimate (as shown in Fig. 1), and assuming comparable trends for different patient groups as a whole, may seem misleading. However, since all reinfection episodes occurred in former IDUs, and these accounted for 81% of the study population, and given the uncertainty of self-reported data on risk-taking

Table 3. Bivariate and multivariate analysis of variables associated with reinfection after treatment-induced SVR.

Variables	Log-rank test		Cox regression analysis	
	Reinfection, n (%)	*p* value	*p* value	Hazard Ratio (95% CI)
Age group		0.16		
<40	9 (8.9)			
≥40 yr	0 (0)			
Sex		0.67		
Male	9 (7.8)			
Female	0 (0)			
Born in Spain		0.07		
Yes	8 (7.0)			
No	1 (20.0)			
Currently on MMT		0.25		
Yes	1 (2.1)			
No	8 (11.1)			
History of IDU ever		0.07		
Yes	9 (9.4)			
No	0 (0)			
HIV infected		0.01	0.01	9.95 (1.73-57.34)
Yes	3 (16.6)			
No	6 (5.9)			
High risk sexual practices		0.14		
Yes	2 (28.6)			
No	7 (6.2)			
IDU during or after treatment		<0.001	<0.001	12.47 (2.90-53.71)
Yes	5 (41.7)			
No	4 (3.7)			
Tattooing during or after treatment		0.57		
Yes	1 (10)			
No	8 (7.3)			
No. of risk factors		<0.001	0.03	7.47 (1.19-46.89)
<2	7 (6.1)			
≥2	2 (40)			

MMT, Methadone maintenance treatment.

behavior, using the entire cohort to illustrate probability of reinfection over time, is a reasonable and conservative approach to highlight the major role of injecting practices in the risk of reinfection based on the available data.

Although the distribution of new HCV genotypes (1 and 3) simply reflects their predominance among drug users in many European countries [27,32,33], whether the frequent genotype switch (7 of 8 cases) was just random or the result of some degree of resistance to reinfection by homologous strains, favoring takeover and persistence of a heterologous genotype, similar to that frequently seen after spontaneous clearance of primary infection, does not seem to confer significant protection against reinfection with the same genotype, subtype or even isolate [34], it is likely that frequent genotype switch observed in the present study occurred by chance. On the other hand, since pre-treatment samples were not available for retesting and baseline subtype was unknown, the possibility that the two cases in which no genotype/subtype switch could be demonstrated represented late relapses rather than reinfections, cannot be excluded. However, since late relapse (beyond six months) after treatment with pegylated interferon and ribavirin is extremely uncommon, and in both cases SVR had been confirmed in two consecutive samples, true reinfection is the most likely explanation. Conversely, although longer testing intervals substantially underestimate reinfection events in IDUs with prior spontaneous HCV clearance [34], it seems unlikely that testing interval significantly underestimated reinfection incidence after treatment-induced HCV clearance in our study. Nonetheless, future studies should schedule shorter testing intervals along with ultra-deep sequencing of HCV RNA-positive samples, to identify transient reinfection events.

Overall, 21% of subjects in our study admitted to engaging in at least one of the predefined risk factors. Relapse in drug use after treatment was admitted by 12 out of 96 former IDUs (12%) after an average follow-up of 1.4 years. Higher relapse rates (33% to 46% after two to five years) after successful HCV treatment have been reported in community IDUs [23,24]. However, in our study, whether reinfection events occurred within or outside prison could not be established, except for the subject who had remained incarcerated during the entire follow-up.

It should be noted that while active IDU during or after treatment was associated with a high reinfection incidence (33.01 cases per 100 person-year), the incidence was 12-fold lower in non-relapsing IDUs (2.57 cases per 100 person-year) and 30-fold lower among never-injecting prisoners (0–1.1 cases per 100 person-year). Although the overall reinfection rate in our study is similar to those previously reported in former or current injecting drug users [23,25,30,31,35] and do not support withholding HCV treatment for IDUs in the prison setting, it seems clear that inmates at risk of IDU relapse should be identified, so that measures aimed at minimizing high-risk injecting practices are implemented before, during, and after treatment [36,37]. In this regard, retention in a methadone maintenance program has been shown to reduce frequency of IDU [17] and of HCV seroconversion [38], and is one of the most widely implemented harm reduction strategies among IDUs within and outside the prison setting [39]. In our study, the proportion of reinfection events among IDUs under MMT was significantly lower than among those not receiving methadone (1/47; 2.1% *vs.* 8/49; 16.3%, respectively; $p = 0.031$), and the only patient reinfected while on MMT was voluntarily leaving treatment and taking a low dose at reinfection. The combined effect of small number of events, differences in follow-up intervals and, especially, under-reporting drug-injecting practices, may explain why the comparison of incidence rates per 100 person-years failed to reflect the low risk of reinfection in MMT-adherent IDUs.

Another opportunity to prevent HCV transmission among IDUs includes adequate implementation of needle and syringe exchange programs. This harm reduction strategy, available at three of the four prisons participating in our study, has been shown to significantly reduce sharing and drug overdoses, without increasing injecting drug practices in prisons, and to be cost-effective in preventing blood-borne infections in injecting drug users [8,9,40].

Since all HIV-positive patients were former IDUs, finding HIV infection independently associated with reinfection might have resulted from a combination of under-reporting drug-injecting practices and small sample size. On the other hand, the possibility of sexually-acquired reinfection from an HCV-infected male partner [41–43], cannot be excluded, since questions regarding receptive anal intercourse were not included in the questionnaire designed for this study. Tattooing, a risk factor for HCV infection in the prison setting [44], although not forbidden, cannot be considered a safe procedure in Spanish prisons, because some tattooing tools are not allowed because of their potentially dangerous misuse. In our study, however, it was not found to be associated with reinfection, although the number of subjects having a tattoo was small.

There are a number of limitations in our study. First, the small number of reinfection episodes and the retrospective nature of the study convey a high degree of uncertainty on reinfection incidence estimates. Hence, reported estimates for the entire cohort and subgroups and forward projections based on estimated cumulative incidence should be interpreted with caution.

Second, since participants had been treated during a seven-year period, the long interval between SVR and epidemiological data collection, as well as potential differences in risk factor assessment by penitentiary physicians conducting the interviews in 2010, might have biased the epidemiological evaluation, limiting reliability of risk behavior data. However, since most participants had been treated during the last four years of the study, the average time elapsed between SVR and interview was 1.4 years. On the other hand, the high rate of participation in the study, the similar proportion of subjects admitting to risk-taking behavior at all participating centers, suggest that personnel conducting the survey did not significantly influence data collection.

On the other hand, our interview did not include details on drug equipment sharing and other high-risk injecting practices or on high-risk sexual practices among non-IDU MSM. Nonetheless, it is unlikely that factors other than those related to drug-injecting practices play a significant role in reinfection risk. In fact, under-reporting ongoing drug-injecting behavior, might not only underestimate the actual relevance of these practices, but could also overestimate the role of other factors on the risk of reinfection. In this regard, patients successfully treated for HCV during prior incarceration, might be more reluctant to report on drug injecting practices, but more prone to over-report alternative risk factors.

Finally, our study population was enrolled upon readmittance into prison and whether they are representative of the entire population of successfully treated inmates remains unknown. This is a relevant issue given the large number of prisoners treated between 2003 and 2009 who achieved an SVR and were not

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in prison during 2010. A simple extrapolation cannot be made because, should re-incarceration rate be higher among relapsing IDUs, persons at high-risk of reinfection would have been over-represented. A simple coordinated retrospective evaluation of a similar sample of prisoners treated during that seven-year period and who were at liberty the first semester of 2010, could quickly provide valuable information to yield more reliable incidence-rates estimates.

Despite its limitations, the study findings strongly suggest that reinfection rates after successful anti-HCV treatment in IDU inmates are unacceptably high, and with the higher costs of current and future DAA-based antiviral regimens, they might argue the cost-effectiveness of providing IDU inmates with shorter and more effective treatments. Hence, immediate actions must be adopted to maximize durability of viral eradication in this patient population. Because HCV reinfection after successful treatment, almost invariably occurs in former IDUs, strengthening preventative measures for those with ongoing or at risk of IDU relapse, should be a priority at diagnosis, and during and after treatment. Such measures should include reinforcing harm reduction strategies combining needles/syringes exchange and MMT, multidisciplinary education and counselling on key issues regarding risk practices, maximizing treatment uptake while in prison and reinforcing retention in community-based treatment programs after release.

Because of differences in penitentiary policies and socio-cultural peculiarities of the incarcerated population, the results of this study may not be generalizable to prison inmates from other developed countries. Notwithstanding, we believe that multicenter prison-coordinated prospective studies to survey the cost-effectiveness of new anti-HCV treatment strategies would make significant contributions to controlling the core of the HCV epidemic in Europe.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2013.03.008.

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