

Reasons for not initiating hcv treatment in prison: a sub-analysis of the epiband study

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ABSTRACT

Objective: This sub-analysis was designed within the framework of the EPIBAND study to establish the reasons why prison patients do not initiate HCV treatment.

Methods: Epidemiological, prospective, multicentre study conducted in 26 centres. We present the results from those patients included in the EPIBAND study who did not initiate HCV treatment for different reasons.

Results: A total of 195 patients were evaluated (average age 39±6.6 years, 86.7% male and 96.9% Spanish nationality). The reasons why this population did not initiate HCV treatment were secondary ones relating to the patient (41%), medical reasons (30.8%), and the prison environment (3.6%). 47.5% of patients reported lack of awareness and motivation, and 18.8% did not initiate treatment as a result of adverse events. Immunological status (35%) as well as psychiatric and neurological disorders (28.3%) were the main medical reasons for contraindication. Aspects associated to prison environment such as impending release or change of prison (64.4%) were among the various reasons that influenced treatment initiation.

Conclusions: Lack of motivation and awareness in patients as well as adverse events were the main reasons for not initiating therapy. These factors are subjective, modifiable aspects that depend on patient education and adequate medical care.

Key words: comparative study; HIV; patients; hepatitis C; therapeutics; prisons; prisoners; Spain.

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INTRODUCTION

The EPIBAND study has been so far the broadest prospective study ever conducted in the prison setting, not only for the number of patients included but also for the number of researchers participating. This epidemiological, prospective and multicentre study has been

implemented by the Spanish Society for Prison Health Group on Infectious Diseases in order to establish the reasons why prison patients discontinue antiviral treatment for hepatitis C. This article aims to describe one of the objectives of the EPIBAND study: establish the reasons why prison patients do not initiate treatment for Chronic Hepatitis C.

The main objective of chronic hepatitis C treatment is its eradication (cure). The efficacy of the current pegylated interferon (INF-PEG) and ribavirin (RBV) combination therapy has been analysed in different studies¹⁻³ and it was found that the rate of sustained virological response (SVR) was 42-51 % for genotype 1 and 76-82 % for genotypes 2-3^{1,3,4}. At present, treatment regimens, according to different variables associated with the virus (genotype, viraemia), the degree of liver injury and on the rate of response to antiviral therapy, allow individualized and optimized treatment.

The prison population presents particularly high rates of HCV infection, prevalence is estimated to be 22.2 % compared to 3 % in the general population⁶. For this reason and because the natural history of hepatitis C virus shows that it is a leading cause of cirrhosis and hepatocellular carcinoma (HCC) as well as the most common indication for liver transplantation⁷, prison population is one of the most suitable cohort to be treated.

This fact highlights the relevance of the disease in this setting, especially within the sub-group of patients co-infected with HIV/HCV⁸ due to associated co-morbidity and a more rapid and progressive clinical evolution.

In theory, incarceration combines a series of characteristics which favour, to a greater extent, the need to provide treatment for this group of patients. Although on occasions treatment can be medically and legally controversial⁹ with this type of patients, it is now however part of the portfolio of standard medical services.

Given the screening for HCV infection carried out on the prison population by means of a serologic study, it is possible to select the individuals that are infected and who are therefore candidates to be treated.

Nearly all the studies show that combined treatment relates a good cost effectiveness¹⁰, since future costs originated by the complications described before can be avoided. Nevertheless, and in order to reach this objective, it is important to optimize treatment taking into consideration that the genotype is the main indicator of virological response, and, following guidelines, to interrupt treatment from week 12¹¹ in patients who do not achieve a 2-log₁₀ reduction in viral load, or in patients HVC-RNA positive at week 24¹² due to treatment failure.

Thus, it is clear that the prison setting has a very large population eligible for treatment, with the most favourable conditions, the necessary resources and with the moral commitment to not forget this

group of potential patients, for the reasons argued above.

Therefore, the circumstances for which patients, sometimes even when it is clearly indicated, do not initiate HCV treatment must be established. This data will help establishing strategies aimed to increase motivation, avoid treatment refusals and give adequate information on treatment and adverse effects, as well as clearly describe the consequences of such refusal. Although the medical team is qualified and the means are appropriate, the decision to initiate treatment depends ultimately on the patients and it is thus essential to increase their motivation and implication regarding their health problem.

It is important to emphasize that the patient and his motivation is not the only challenge to be faced, and where action is needed. The prison setting also greatly hinders treatment. Thus, while on some occasions it is the continuous transfers between centres that condition its continuity, on other occasions, it is the proper health care structure, with inadequate medical resources, poor coordination with the hospital of reference and/or delay in diagnostic tests, and, occasionally, a lack of sensitivity from the medical staff regarding this matter.

Nevertheless, there are times in which it is all about the clinician himself, including the patient's interest, even though treatment toxicity conditions and contraindicates its initiation¹³. Therefore, selection of patients is indispensable in order to enable treatment adherence, avoid serious adverse effects and eventually lead to success.

MATERIAL AND METHODS

Design of the study

The present analysis was designed within the framework of the EPIBAND study. It is an epidemiological, prospective, multicentre study in which 26 prisons throughout Spain participated. Authorisations have been obtained from the organization of Prison Health physicians within the Sub-Directorate General for Prison Health, the General Directorate of Correctional Institutions of the ministry of the Interior and the Serveis Penitenciaris, Rehabilitació i Justícia of the Department of Justice of the Generalitat of Catalonia. Approval has also been requested to the Ethics Committee of Clinical Research at Reina Sofía Hospital in Cordoba. The study has been conducted in accordance with the International ethical recommendations (Declaration of Helsinki and Oviedo agree-

ment law), clinical guidelines for best practice, Royal Decree 711/2002, as well as the legislation in force in Spain at the beginning of the study, to carry out observational studies (circular 15/2002). Processing, communication and transfer of personal data of all participants comply with organic law 15/1999 of 13 December on the protection of personal data.

Procedure

Between October 2007 and July 2008 patients who were included had previously been diagnosed with chronic hepatitis C, with serologic evidence of infection after anti-HCV test, naïve-patients for ribavirin and interferon and detectable plasma HCV RNA levels. All the participants have been previously informed of the objective of the study and were asked to give a signed informed consent document in accordance with the strictest ethical guidelines¹³. The study was conducted in real-life health care conditions and following the usual clinical practice of the participating institutions.

The sample for this analysis is made up of patients who for different reasons, among the population included in the EPIBAND study, did not initiate antiviral treatment during the inclusion period established in 9 months. This sub-analysis does not follow the prospective design of the EPIBAND study, but is a cross-sectional survey, taken right at the moment of the basal visit, of the reasons why certain patients, who have been included in the study, do not initiate treatment.

The data needed to reach our objective were obtained from the participants' medical records as well as from the information provided by the medical teams in each institution and by the patients themselves.

Variables

The following variables were studied: age, sex, weight, nationality, HCV viral load, genotype, HIV, fibrosis diagnosis tests and stages by means of biopsy and fibroscan®.

The reasons why patients did not initiate treatment were also collected, including medical reasons (contraindications according to medical literature), secondary ones relating to patients and the prison environment.

The secondary reasons relating to patients considered subjective variables that patients could put forward in order not to initiate treatment, such as lack of motivation and awareness, fear of adverse

effects, lack of confidence in the health professionals as well as influence of relatives or other inmates. The secondary reasons relating to the prison environment include factors involving the prison environment as a distorting element which could be an impediment to treat patients, among which lack of material resources, human/health professional resources and impending release/transfer to another centre.

STATISTICAL ANALYSIS

Quantitative variables were analysed with both centralization and dispersion measures. Specifically, parametric statistics are expressed as mean \pm standard deviation and the non-parametric as median and percentile.

Qualitative variables are presented using relative and absolute frequencies. The distribution of relative frequencies is expressed in valid percentages and correspond to the calculation related to valid total, number of patients who really present data in the variable excluding missing values.

The statistical analysis was carried out in SPSS version 17.0.

RESULTS

The EPIBAND study included a total of 636 patients, of which 431 initiated treatment with peginterferon alfa-2a and ribavirin, and 205 did not initiate chronic hepatitis C treatment. Below are the results of the analysis corresponding to the group of patients who did not initiate antiviral treatment. Of the 205 patients who did not initiate treatment, 195 were evaluable patients. 10 patients who did not have genotype or viral load (N=4), or did not have genotype but negative viral load (N=6) were removed from the analysis. Table I shows the socio-demographic and clinical characteristics.

Mean age of patients was 39 \pm 6,6 years, 86.7 % were male, and 96.9 % were Spanish. Among the clinical variables analysed, 66.5 % of patients presented a high viral load, defined as \geq 400.000 UI/ml. Genotype distribution showed the prevalence of genotype 1 in 55.9 % of patients followed by genotype 3 in 23.7 % of them. Genotypes 4 and 2 were less common, with a percentage of 18.3 % and 2.2 % respectively. 40 % of patients presented co-infection with HIV. Of the HIV co-infected patients, 30.1 % of them were genotype 1/4, and only 28 % showed high viral load. 4 % of patients had undergone a biopsy and 22.8 % a fibroscan®.

	N= 195
Age-years; mean (\pm SD)	39 (6,6)
Sex-M/F; (% men)	169/26 (86,7)
Weight-kg; mean (\pm SD)	72,8 (12,5)
Nationality; n (%)	
Spanish	189 (96,9)
Other	6 (3)
HCV-RNA; n (%) ^a	
\geq 400.000 UI/ml	125 (66,5)
< 400.000 UI/ml	63 (33,5)
Genotype; n (%) ^b	
1/4	138 (74,2)
2/3	48 (25,8)
HIV; n (%)	78 (40)
Diagnostic tests; n (%)	
Biopsy	7 (4)
Fibroscan®	43 (22,8)
Degree of fibrosis by biopsy; n ^c	
No fibrosis	1
F1-F2	2
F3-F4	2
Degree of fibrosis by Fibroscan®; n (%) ^d	
No fibrosis	4 (9,8)
F1-F2	27 (65,9)
F3-F4	10 (24,4)

SD: Standard Deviation;

Missing data: ^a n=7; ^b n=9; ^c n=2; ^d n=2.

Table I. Socio-demographic and clinical characteristics.

Prevalence for the different stages of fibrosis according to biopsy was 20 % for degrees F0-F4. By means of fibroscan®, these percentages were 9.8 %, 48.8 %, 17,1%, 17,1% and 7,3% for F0, F1, F2, F3 and F4 respectively.

With regards to the reasons for not initiating antiviral treatment, it is important to stress that medical reasons and secondary ones relating to patients were considered excluding reasons, that is to say, they may not appear in the same patient in contrast with secondary ones relating to both patients and the prison environment.

Results showed that the most relevant reasons for not initiating treatment were the secondary ones relating to patients in 80 (41 %) cases, and medical reasons in 60 (30.8 %) cases. Secondary reasons relating to both the prison environment and patients were exposed by a total of 55 patients, of which 48

(24.6 %) reported only those relating to the environment and 7 (3.6 %) patient expressed secondary reasons relating to both patients and the prison environment in order not to initiate treatment (Figure 1).

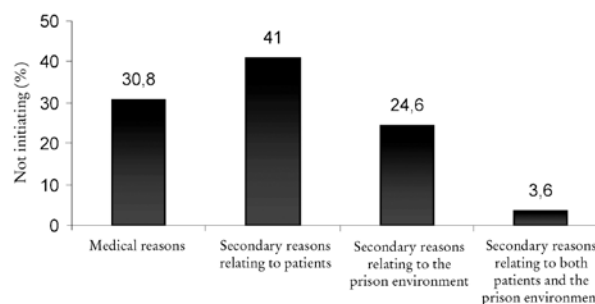


Figure I. Reasons for not initiating antiviral treatment.

The detailed analysis regarding the secondary reasons relating to patients is shown in Table II. Specifically, lack of motivation and awareness of the patient, with 47.5%, was the main reason not to undergo treatment. Adverse effects, although in a lower percentage, 18.8%, was also an important reason not to undergo treatment. In that sense, the most feared adverse effect was depression in 53.3% of patients, followed by weight loss in 46.7% of them and irritability in 26.7%.

Reasons for not initiating antiviral treatment	N (%) [*]
Lack of motivation / awareness of the patient	38 (47,5)
Lack of motivation / awareness of the patient and fear of adverse effects	16 (20)
Fear of adverse effects	15 (18,8)
Influence by relatives/other inmates	5 (6,3)
Lack of motivation / awareness of the patient and influence by relatives/other inmates	3 (3,8)
Lack of confidence in the health professionals	2 (2,5)
Others	1 (1,3)
Total	80 (100)

*Valid percentages

Table II. Secondary reasons relating to patients.

Regarding medical reasons, 60 patients (30.8 %) did not initiate chronic hepatitis C treatment in line with the physician's evaluation (Table III). According to medical literature, within the contraindications associated with antiviral treatment, immunological status was the main cause for not initiating treatment in 35 % of cases. Psychiatric and neurological disorders, as well as other pathologies were causes of contraindication in 28.3 % and 21.7 % of cases respectively.

Contraindication according to medical literature	N (%) [*]
Immunological status	21 (35)
Psychiatric / neurological cause	17 (28,3)
Other pathologies	13 (21,7)
Mild fibrosis/Low VL-viral HCV	5 (8,3)
Drug use	3 (5)
Pregnancy	1 (1,7)
Total	60 (100)

^{*}Valid percentages

Table III. Medical reasons

The analysis of secondary reasons relating to the environment showed the prison setting as an impediment to treat patients. Thus, patients' impending release or transfer to another centre was another reason for not initiating treatment in 31 patients (64.6 %), and lack of material resources in 1 patient only (2.1 %). The rest of secondary reasons relating to the prison environment, and which represent 16 cases (33.3 %), were all due to delays in diagnostic tests with fibroscan ® and/or biopsies.

Finally, it must be stressed that in 7 cases (100%), a close relation between reasons relating to patients and those to the environment, such as the lack of motivation or awareness together with impending release or transfer to another centre, was observed and which contributed to the same degree in the decision to not initiate treatment, this type of patient was considered as an independent sub-group.

DISCUSSION

The results concerning the socio-demographic and clinical variables of the population studied are similar to those found in the general population: male, about 40 years of age, genotype 1 with high viral load, and mono-infected population. Nevertheless, and despite the decline in the prevalence of HIV/HCV co-infection in Spanish prisons¹⁴, our work shows a high proportion (40 %) of co-infected population, data which is different from the population outside prison.

The main circumstance for patients not to initiate treatment is in line with the secondary reasons relating to patients in 41 % of cases. These reasons include all the subjective variables that patients can put forward in order not to start treatment, such as lack of motivation and awareness, that is to say, lack

of strength or energy to start a lengthy treatment, maintain adherence to it and cope with the adverse-effects that may appear. The inability to evaluate the consequences that this silent disease can cause in the medium and long term has also been included. With 47.5 % of cases, it is the most generalized response or excuse, and perhaps the most closely linked to a lack of information, or inaccurate information. The silent nature of the disease generates little concern and thus patients minimize its risks and relevance. 18.8 % of patients reported fear of adverse effects in addition to the previous circumstances, maybe the most feared and known variable to all¹⁵.

It is clear that this lack of motivation is the main reason for refusing treatment and it relies on many factors such as knowledge regarding the health problem, level of communication with the physician or accessibility to the health team. Patients need to perceive security, care, follow-up and solution to adverse effects associated to the disease and ultimately a protective environment to ensure treatment adherence and continuity.

More specifically, neuropsychiatric adverse effects such as depression and irritability are the most noticeable and also represent one of the most common causes of treatment withdrawal¹⁶⁻¹⁸. If, in addition to being in prison, patients show bad mental health, adverse effects are likely to be one of the main reasons for not initiating treatment. In addition, and although to a lesser extent, weight and hair loss must be mentioned since they are among the most feared adverse effects, with 46.7 % and 6.7 % respectively. It is important to keep in mind that management of adverse effects must start even before initiating treatment, thus creating confidence, truthfulness and the necessary information to overcome adverse effects as soon as they appear.

On other occasions, the patient's decision is influenced by external factors. Relatives' or other inmates' opinion sometimes advises patients against starting treatment and this aspect accounted for 3.8 % of cases in our study. To avoid this, it is important to make contact with the relatives at the moment of initiating treatment and to make them understand how treatment adherence and completion is important. The patients themselves at certain times ask us to give their relatives basic information regarding treatment and visible adverse effects that they are likely to notice.

Lack of confidence in the health professionals is experienced by 2.5 % of patients, which represents a very low incidence in our study. This variable was studied in order to establish if the decision not to be treated could be due to low credibility and/or capacity

of the prison health care system. This result highlights that confidence is high, care provided meets the expectations and that imprisonment is not an impediment to initiate treatment. Finally, we have included an option open to other considerations that had not been raised at first in the secondary reasons relating to patients in response to a single case who requested psychoactive drugs as a condition to start treatment.

On the other hand, 30.8 % of total cases reported medical reasons or formal contraindications, according to medical literature for the initiation of hepatitis C treatment. Immunological status was the most common cause in regard to HIV with 35 % of cases and particularly the level of CD4, followed by neuropsychiatric disorders in 28.3 % of cases, specially due to depression, impulse control and behaviour disorders, psychosis and epilepsy. These two factors define the profile of our patients, therefore it stands out that they can be regarded as the main reasons for medical contraindication.

In addition to this, with 21.7 % of cases, a connection with other pathologies, which are currently contributing to contraindications, was reported, mild fibrosis/low viral load in 8.3 %, active drug use in 5 % and pregnancy in 1.7 %. It must be stressed that all the contraindications observed during the study could be considered relative or circumstantial and that patients, after having gone over them, stabilize and normalize and could start hepatitis C treatment without medical contraindication being a barrier. The variability and extent of the pathologies in this sub-group is also particularly striking. Thus, what can be considered a formal contraindication to some professionals, can be an indication in all aspects to others. Without a doubt, this aspect is in harmony with the styles of the reference hospital, as well as with the experience and management in the treatment of this illness.

Finally, secondary reasons relating to the environment represent 24.6 % of total cases. The prison setting itself acts as a distorting element which prevents patients from initiating therapy and release from prison or transfer to other centres is reported in the majority of cases, in 64.6 % of them. It is important to know that classification of inmates relates more to regimental, legal or treatment criteria than that of a medical nature, therefore this eventuality is rarely shared with the Direction of the institution which carries out patients' transfers.

Delay in complementary testing such as biopsy or fibroscan® hinders treatment initiation in 33.3 % of cases. This aspect is also a variable circumstance in connection with referral hospitals, management of out-patient appointments or waiting lists, as well as

complementary testing protocols. In 3.6 % of total cases, a link between secondary reasons relating to patients and those relating to the prison environment has been established, specifically connected to impending release and lack of awareness in patients. There is no need to further develop these facts, since they have largely been described.

By means of conclusion, it is important to highlight that lack of motivation and awareness in patients as well as adverse effects were the main reasons for not initiating chronic hepatitis C therapy. These factors are subjective and modifiable aspects that depend on the patient's education and training as well as adequate medical care.

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