Open

Microenvironment Eradication of Hepatitis C: A Novel Treatment Paradigm

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OBJECTIVES: **Prisons are major reservoirs of hepatitis C virus (HCV) in which a therapeutic approach has been particularly difficult so far. Our aim was to create a permanent program of HCV elimination in a prison based on a "test and treat" strategy.**

METHODS: **This open-label clinical trial was conducted in the Spanish prison "El Dueso" between May 2016 and July 2017. Viremic patients were treated with a ledipasvir–sofosbuvir regimen (8–12 weeks) according to the 2015 Spanish Guidelines. A teleconsultation program was established to follow-up patients from the hospital. Non-responders were submitted for a phylogenetic analysis and offered retreatment. An evaluation of new cases of HCV infection was performed every 6 months and upon release in all inmates.**

RESULTS: **847 (99.5%) inmates accepted to participate. HCV antibodies were present in 110 (13.0%) and 86 (10.2%) had detectable viremia. Most of them were genotype 1 or 3 (82.6%) and had <F2 fibrosis (52.2%). Treatment was started in the 69 inmates whose stay in prison was longer than 30 days. Sustained virological response was achieved in 64 out of 66 patients (96.9%), three of whom were successfully rescued with a salvage regimen after treatment failure. Two patients were lost to follow-up and three are currently on treatment without viremia. As a result, by July 2017 none of the 409 imprisoned was viremic, and neither reinfections nor de novo infections were detected.**

CONCLUSIONS: **A sustained "test-and-treat" strategy against HCV in prisons is feasible and beneficial. Spreading this strategy should entail a public health impact.**

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INTRODUCTION

Hepatitis C virus (HCV) is a leading cause of liver-related morbidity and mortality worldwide, especially in Mediterranean countries where prevalence rates range from 1 to 3% in the general population [1]. In Spain, the latest population-based data collected during 2016 estimated anti-HCV and viremic (HCV-RNA detectable) prevalences lower than expected (1.2 and 0.4%, respectively) [2, 3].

The problem is exacerbated in prisons and other closed settings (i.e. jails, pre-trial detention centers, psychiatric institutions, etc.), where a high prevalence of risk behaviors, mainly injection drug use (IDU), is associated with a nearly ten times higher prevalence of HCV infection than that of the general population [4]. Accordingly, a recent observational study carried out in 2011 on 18 Spanish prisons revealed a prevalence of HCV infection of 22.7% [5]. Seroprevalence in Western European and US prisons is slightly

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lower (15.5% and 15.3%, respectively) [6]. Some intrinsic circumstances aggravate the problem, such as a substantial risk of HCV transmission during incarceration and after release, favored in part by an unawareness rate up to 25% [7].

Testing HCV in high-risk populations and subsequently treating the infected populations has been recommended for years as an epidemiological prevention measure to control a widespread infection, and also to prevent disease injury on an individual basis [8]. However, there have been several classical barriers that have limited the universality of these policies [4, 9]: lack of treatments with high beneficial/risk ratios and costs of treatments that influence on healthcare budgets of closed settings; penitentiary health care managed within each country by public agencies with different sensitivity to the health problem posed by prisons; persistence of indoor risk practices favouring intraprison transmission; limited capacity to access hospital-based hepatitis specialists; lack of specialist nurses; complex health care needs of prisoners; high detainee turnover, etc. The advent of powerful and safe direct-acting antivirals (DAAs) in the last years, and the implementation of more rational penitentiary policies in terms of prevention and healthcare access must aid to face these challenges [10].

It has been recently advocated that a strategy based on "micro-elimination" programs targeted on risk populations like prisoners may allow authorities to achieve the World Health Organization (WHO) commitment of eliminating viral hepatitis B and C as public health threats by 2030 [11]. Up to now, there have been some experiences of epidemiological surveillance and even treatment programs in selected prisons [7, 12]. Nevertheless, they all lack generalization or even maintenance of these programs, probably due to the aforementioned barriers.

The objective of this study was to design and evaluate a project for the elimination of HCV in a penitentiary center through the development of a sustained health care model based on three premises: (1) the creation of true multidisciplinary teams to care for infected inmates, (2) a universal screening and treatment strategy with DAAs, and (3) the use of telemedicine as a support tool.

METHODS

Study design and population

This was an open-label, single-arm, phase-IV clinical trial of low-grade of intervention (Clinicaltrials.gov Identifier: NCT02768961). It was carried out between May 2016 and July 2017 in the penitentiary center of "El Dueso" in Santoña (Cantabria, Spain).

The program was directed to the whole inmate population imprisoned during this period (i.e. both the baseline population at the beginning of the study and all new admissions). Age higher than 18 and acceptance to participate were the only eligibility criteria.

Phases of the project and professional network

The project was carried out on the basis of a multidisciplinary collaboration between the prison and the Valdecilla University Hospital. It was structured into five phases (Fig. 1). The *first phase* consisted of creating a multidisciplinary professional network and defining the specific relationships between the different agents involved (Fig. 2). The team was coordinated by hepatologists and was supported by an expert on telemedicine. The *second phase* consisted of recruiting the inmates and performing a universal screening of viral diseases. Every patient was asked to participate in the study, and if they agreed, they signed the informed consent. At baseline, variables including anthropometrics, demographics, risk behaviors, medical history, particularly if related to HCV infection and psychiatric conditions, were recorded. A serum sample that included a complete blood cell count, biochemistry and viral markers (HBsAg, anti-HBs, anti-HBc, anti-HCV and anti-HIV) was also obtained. Quantification of hepatitis B virus DNA was determined in HBsAg positive individuals by polymerase chain reaction.

HCV infection characterization (i.e. viremia and genotype, clinical and pharmacological history, ultrasonography and FibroScan® -Echosens™ NorthAmerica; 1050 Winter Street, Waltham, MA 02451, USA-), and the subsequent systematic treatment of viremic patients were performed in the *third and fourth phases* of the study, respectively. Finally, a *fifth phase* of follow-up was implemented in order to maintain the program over time and to detect new incident cases of HCV (i.e. intraprison transmission). Thus, all new admissions were proposed to participate in the program, and the whole population study, infected or not at baseline, were re-evaluated every 6 months and upon release, and any relapse or new infection was offered to be treated. In addition, a strategy of follow-up was planned for those treated patients who left prison, either because they were transferred to another prison, or because they reached freedom. In the former group, health care providers at El Dueso contacted their colleagues at other centers to gather information, whereas in those released follow-up was performed in our hospital.

Interventions

Every chronic infected patient whose stay in prison was expected to be longer than 30 days was offered treatment in accordance with the Spanish National Strategy Plan for the Hepatitis C (SNSPHC) in force at the beginning of the study [13]. In order to assure adherence two main decisions were adopted: (1) to treat every patient with the simplest antiviral regimen based on a fixed-dose combination tablet containing 400 mg of sofosbuvir and 90 mg of ledipasvir (Gilead Sciences, Inc., Foster City, CA 94404), administered orally once daily without ribavirin. This combination was selected according to the aforementioned Spanish guidelines and taking into account the specific availability of antiviral drugs during the study period in our region. This policy was established by the regional Department of Health, and for example, precluded the prescription of other schemes (i.e. sofosbuvir+daclatasvir for genotype 3). Therefore, the industry financial support in the study did not influence in any way the decision to treat patients with this single DAA combination. Treatments were prescribed by one hepatologist and lasted 8–12 weeks according to the characteristics of the disease; (2) to administer the therapy under direct observation supervised by the staff from El Dueso health department. During the periods in which detainees were out of prison, a counting pill and a direct interview were established for assessing compliance.

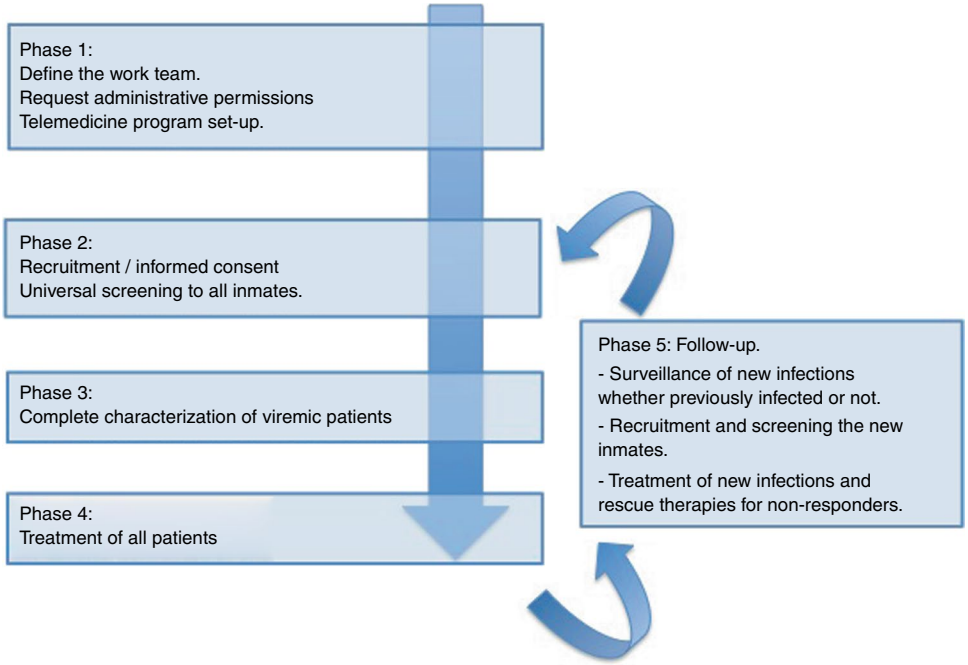

Fig. 1 Phases of the study

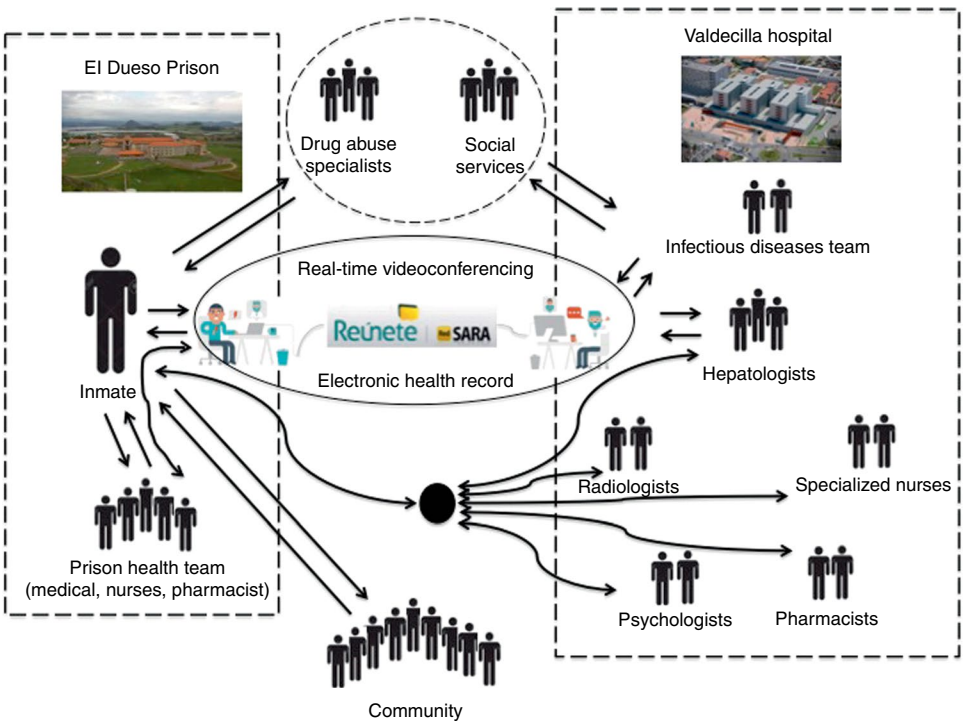

Fig. 2 Schematic representation of the multidisciplinary professional network created to care the inmate population. "Reúnete-Red SARA" refers to the video collaboration tool, available to all public administrations in Spain (https://administracionelectronica.gob.es/ctt/redsara#.WOjGTJQhXqA), which served as a teleconsultation tool and a service of virtual meetings

Follow-up

A teleconsultation program between the prison and the hospital was established to follow-up patients and monitor therapy. It was established by the video collaboration tool "Reúnete-Red SARA", available to all public administrations in Spain [14]. Thus, face-to-face consultations at the hospital were replaced by teleconsulta-

Table 1 Telemedicine satisfaction assessment through a self-administered questionnaire based on a 5-point Likert scale

Question		Score	
		Mean	SD
Q1	I was able to see the doctor through the screen	4.5	0.6
Q2	I was able to hear the doctor well through the speakers	4.2	1.1
Q3	The doctor could hear me without trouble	4.4	0.8
Q4	I felt comfortable talking to the doctor through the screen	4.6	0.9
Q5	When I started the consultation I was not more nervous than usual	4.0	1.4
Q6	During the consultation I was relaxed	4.5	1.2
Q7	I could explain what I wanted to the doctor	4.5	1.2
Q8	I understood the instructions the doctor gave me	4.7	0.5
Q9	I am in accordance with the timeliness of consultation	4.2	1.3
Q10	My privacy and confidentiality was respected	4.6	1.4
Q11	Overall, I am satisfied with the service received	4.7	0.6

Each question was scored through a 5-point Likert scale:
1: strongly disagree, 2: disagree, 3: neither agree nor disagree, 4: agree, 5: strongly agree. Questions that scored >4 points indicate high level of satisfaction.
SD standard deviation, *Q* question

tions (baseline, week 4, end of treatment "EOT" and 12, 24 and 48 weeks after EOT). This tool not only served as a simple teleconsultation between patient and physician as previously described in this setting, but was also used to develop a complete interprofessional network of assistance [15]. Quality and satisfaction of teleconsultations were evaluated through a self-administered questionnaire divided into 11 questions, each of them being assessed by a 5-point Likert scale (Table 1). Finally, all adverse events (AEs) were recorded and serious AEs were monitored throughout the study. All AEs were coded using the Medical Dictionary for Regulatory Activities.

Outcomes

Primary endpoint. The primary objectives were to determine the prevalence of HCV viremia at July 23, 2017, and the incidence of new cases of HCV infection (i.e. intraprison transmission) during the study period.

Efficacy assessments. Plasma HCV-RNA levels were measured with the use of the COBAS TaqMan HCV-RNA assay, version 2.0 (Roche Molecular Systems, Pleasanton, CA), with a lower limit of quantification of 25 IU per milliliter and a lower limit of detection of 10 IU per milliliter. HCV-RNA levels were measured at baseline, at weeks 4, 8, 12, and at the follow-up visit held 12 weeks after EOT. A sustained virologic response (SVR) was defined as a viral load <10 IU per milliliter 3 months after EOT.

Phylogenetic analysis. Phylogenetic analysis of the nucleotide sequences obtained was carried out in order to investigate any possible epidemiological linkages among patients that could help to distinguish between persistent infection, reinfection, and super-infection. Consequently, blood samples were obtained for viral sequencing at baseline and at any time during or after EOT in those patients who either did not meet the criteria for a SVR, experienced a breakthrough, a relapse, or those who became viremic after achieving a documented SVR. Part of hypervariable region 1 (HVR1) of the hepatitis C genome was amplified and sequenced in samples from all HCV RNA-positive patients. The HVR1 fragment (nucleotide positions 1156–1234) was chosen for sequence analysis because this domain exhibits a sufficiently high degree of variability to allow analyses to distinguish between HCV isolates of the same subtype. The HVR1 fragments isolated from the patients were aligned by using the SeaView program [16, 17].

Sample size. The study was intended to test the whole inmate population and to treat all chronic infected patients who accepted to participate. Therefore, no sample size was calculated.

Patient involvement. Prisoners were involved in some parts of the design of the study. Thus, some informative meetings were carried out between the investigators, prison health care providers and the inmate population before defining the protocol. These meetings served to explain the importance of different epidemiological preventive measures against infectious diseases and the current opportunities of treatment against HCV chronic infection. Two major decisions were taken after explaining the design and discussing it: to definitely accept telemedicine as a consultation tool and to use the shortest regimens avoiding the use of ribavirin.

Ethics. The study was approved by all Institutional Review Boards (IRB) and by the Ethics Committee of Cantabria (act 20/2015) and was conducted in compliance with the Declaration of Helsinki and International Conference on Harmonization guidelines. A designated member of the IRB was in charge of monitoring the trial in order to ensure independence, autonomy, and justice in this environment. Periodical visits to the investigators and even to the penitentiary center were consequently scheduled. Throughout the study prisoners were free to question the investigators and to refuse to participate without any repercussions during the incarceration period. All patients included signed a written informed consent provided before enrollment.

Statistical analysis. A descriptive analysis was performed. Categorical variables were described with percentages, and continuous variables were described with mean and standard deviation or median and range/interquartile range (IQR) as appropriate. A 95% confidence interval (CI), was used to estimate proportions. The statistical analysis was performed with SPSS Statistics for Windows, Version 21.0 (IBM Corp, Chicago, Armonk, NY, USA). All p-values were two-tailed. Statistical significance was defined as $p < 0.05$.

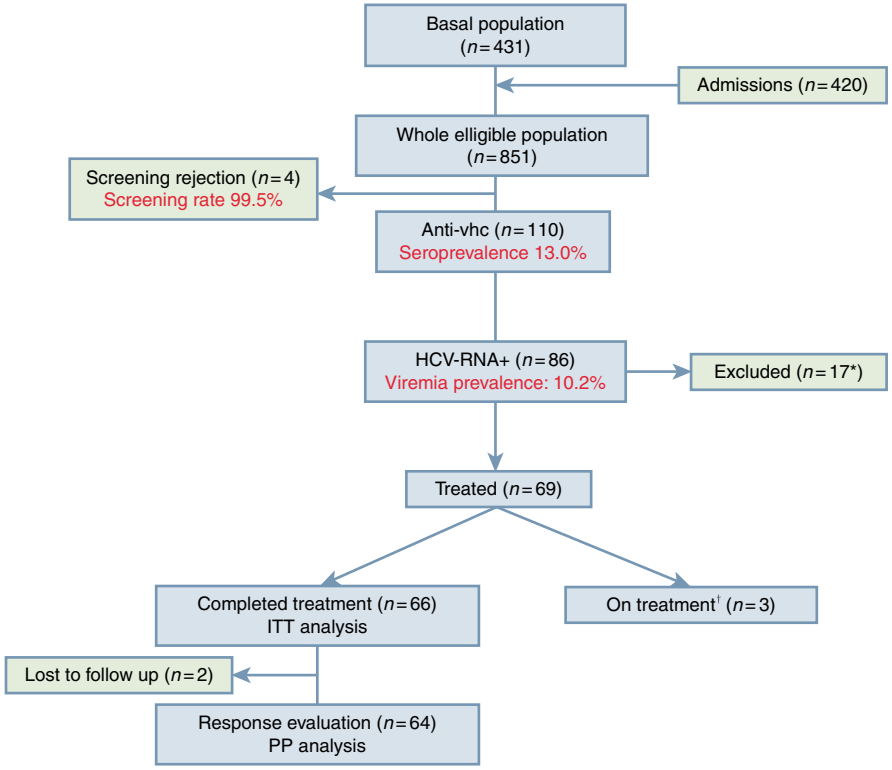

Fig. 3 Flow-chart of the study. *Patients whose confinement period at the center was expected to be lower than 30 days were excluded of the fourth (treatment) phase of the study. They were informed of their disease and possibilities of treatment in other centers or after leaving the prison. †Refers to those patients who were either on treatment or waiting for a SVR confirmation. *ITT* intention to treat, *PP* per protocol

RESULTS

Characteristics of the study population

An offer to participate was given to 851 inmates (420 of them represented new admissions during the study period) (Fig. 3). Baseline and new-admitted inmates had similar demographic, clinical, and virological characteristics. Only four inmates (0.5%) refused to participate. All the participants were Caucasian with a median age of 36 years (range 18–78 years) and most of them were male (95.9%). Sixty-five inmates (7.6%) were active IDU and followed a needle exchange program in prison, whereas 57 (6.7%) were on opioid substitution therapy. Table 2 shows the demographic, clinical, and virological characteristics of both the whole inmate population and those chronically infected. HCV antibodies were present in 110 inmates (13.0; 95 CI, 10.9–15.4%), being this proportion higher in the IDU population (47.7; 41.2–54.3%). Overall, 86 (10.2; 8.3–12.4%) had detectable HCV-RNA (11 of them being co-infected with HIV). Therefore, 78.2% of seropositive inmates were viremic. Most chronic HCV patients had genotypes 1 or 3 (82.6%) and presented a low fibrosis stage (F0–F1, 52.2%), although 25% were cirrhotic (Table 2).

Efficacy and safety

Seventeen out of 86 viremic patients whose confinement period at the center was expected to be lower than 30 days were excluded from the treatment phase. They were informed of their disease and of the feasibility of treatment once outside. The remaining 69 viremic patients accepted and started the treatment. The majority of patients ($n=65$, 94.2%) were treated for 12 weeks (Table 2). All HIV co-infected patients were on highly active antiretroviral therapy and no changes in their regimen were made while on DAA treatment. At the time of this writing, 66 out of 69 patients have completed the scheduled treatment. Two of them were lost to follow-up upon their release from prison (both of them had already finished the treatment and they had showed EOT response). The remaining three patients are currently on treatment and all of them have undetectable viremia so far. Of the 64 patients with an evaluation of the response, only three were non-responders (Fig. 4). SVR was 92.4% (83.5–96.7%) by intention to treat analysis and 95.3% (87.1–98.4%) by per-protocol (PP) analysis. All failures consisted of viral breakthrough during treatment in naïve, genotype 3 patients with different stages of fibrosis (F2 or F4). Two of them were HIV co-infected. All three cases had been treated for 12 weeks and had exhibited a correct adherence to the treatment (≥90%). Phylogenetic analysis showed that all the cases analyzed were recurrences and not reinfections. They were successfully rescued with a 12-week length salvage regimen (sofosbuvir, elbasvir/grazoprevir, and ribavirin) yielding an average SVR of 96.9% (89.6–99.2%) by ITT. The mean treatment adherence throughout the study was 99.3% (SD = 2.3%). Seven patients obtained a 3-day legal permission to leave prison while they were on treatment. All of them received the medication for that period, declared to have taken it correctly, returned the empty blister-packs, and reached a SVR.

Table 2 Baseline characteristics of (A) the whole inmate population included from May 2016 to July 2017 and (B) inmates with chronic hepatitis C virus infection who initiated treatment

	(A) Whole cohort[a]	(B) Chronic HCV[b]
No.	847	69
Age, median (range), year	36 (18–78)	44 (19–61)
Male, no. (%)	813 (95.9)	67 (97.1)
BMI, mean (SD), kg/m^2	25.3 (3.9)	25.3 (5.0)
Time of reclusion, median (range), weeks	270 (4–1.026)	245 (6–1.026)
Current or previous IDU, no. (%)	220 (25.9)	64 (92.7)
IDU on a syringe exchange program, no. (%)	65 (7.6)	13 (18.8)
Opioid substitution therapy, no. (%)	57 (6.7)	23 (33.3)
Active smoke habit, no. (%)	703 (82.9)	64 (92.8)
History of alcohol abuse, no. (%)	123 (14.5)	36 (52.2)
Comorbidities, no. (%)		
Psychiatric disorders	155 (18.3)	30 (43.5)
Diabetes mellitus	33 (3.9)	6 (8.7)
Dyslipemia	59 (6.9)	8 (11.6)
Hypertension	69 (8.1)	6 (8.7)
Anti-HIV+ve, no. (%)	21 (2.5)	11 (15.9)
HBsAg+ve, no. (%)	4 (0.5)	0 (0)
Anti-HBc+ve, no. (%)	90 (10.6)	22 (31.9)
Anti-HCV+ve, no. (%)		
General population	110 (13.0)	69 (100)
Subjects with previous or current IDU	105 (47.8)	64 (100)
Detectable HCV RNA, no. (%)[c]	86 (10.2)	69 (100)
Coinfection rate, no. (%)		
HIV[d]	11 (1.3)	11 (15.9)
HBV	0 (0)	0 (0)
HIV-HBV[e]	1 (0.1)	0 (0)
Baseline HCV RNA [$\log_{10}$ IU/mL, median (IQR)]		5.9 (5.5–6.4)
HCV genotype, no. (%)		
1/1a		20 (29.0)
1b		9 (13.0)
3		28 (40.6)
4		12 (17.4)
Fibrosis stage distribution (Fibroscan)		
F0–1		36 (52.2)
F2		9 (13.1)
F3		7 (10.1)
F4		17 (24.6)
HCV treatment experienced, no. (%)		15 (21.7)
Analytical parameters (median [range])		
Alanine aminotransferase (U/L)	39 (9–401)	67 (10–401)
Total bilirubin (mg/dL)	0.5 (0.2–2)	0.6 (0.2–2)
Albumin (g/dL)	4.5 (3.2–4.9)	4.3 (3.2–4.9)
Creatinine (mg/dL)	0.9 (0.3–2.2)	0.8 (0.3–1,17)
INR	0.9 (0.8–2.2)	1.1 (0.9–1.5)
Platelet count, $\times 10^9$/L	185 (36–380)	177 (36–344)
MELD, median (range)		9 (6–13)
DAA regimen		
Ledipasvir/sofosbuvir 8 weeks, no. (%)		4 (5.8)
Ledipasvir/sofosbuvir 12 weeks, no. (%)		65 (94.2)

HCV hepatitis C virus, *BMI* body mass index, *IDU* injection drug use, *anti-HIV* antibodies against human immunodeficiency virus, *HBsAg* hepatitis B surface antigen, *anti-HBc* antibodies against hepatitis B core antigen, *anti-HCV* antibodies against hepatitis C virus, *RNA* ribonucleic acid, *HIV* human immunodeficiency virus, *HBV* hepatitis B virus, *INR* international normalized ratio, *MELD* model for end-stage liver disease, *DAA* direct-acting antiviral agents
[a]Refers to the sum of all inmates detained at the beginning of the study or baseline inmate population ($n=431$) and all new admissions until July 2017 ($n=420$)
[b]Refers to those chronic HCV infected who initiated treatment (17 patients were excluded; see text)
[c]Plasma HCV RNA levels were measured with the use of the COBAS TaqMan HCV RNA assay, version 2.0 (Roche), with a lower limit of quantification of 25 IU per milliliter and a lower limit of detection of 10 IU per milliliter
[d]Refers only to patients with active HCV infection
[e]Refers to an HIV co-infected patient on HAART, with a previously cured HCV infection (responsive to a pegylated interferon and ribavirin regimen), and with a non-detectable HVB viremia under tenofovir treatment

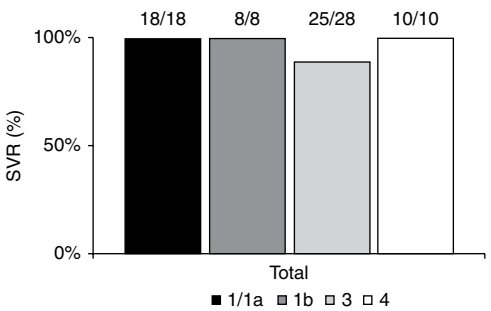

Fig. 4 Sustained viral response (SVR) according to HCV genotype. Only response to the first scheduled regimen (sofosbuvir+ledipasvir) is considered

Two patients had to be hospitalized because of hepatic decompensation (variceal hemorrhage and ascites, respectively), but they could return to prison and resume the treatment after being appropriately treated. Both were genotype 1 cirrhotic patients with the following baseline characteristics: MELD score (12/12); platelet count ($67/70 \times 10^9$/L) and albumin serum levels

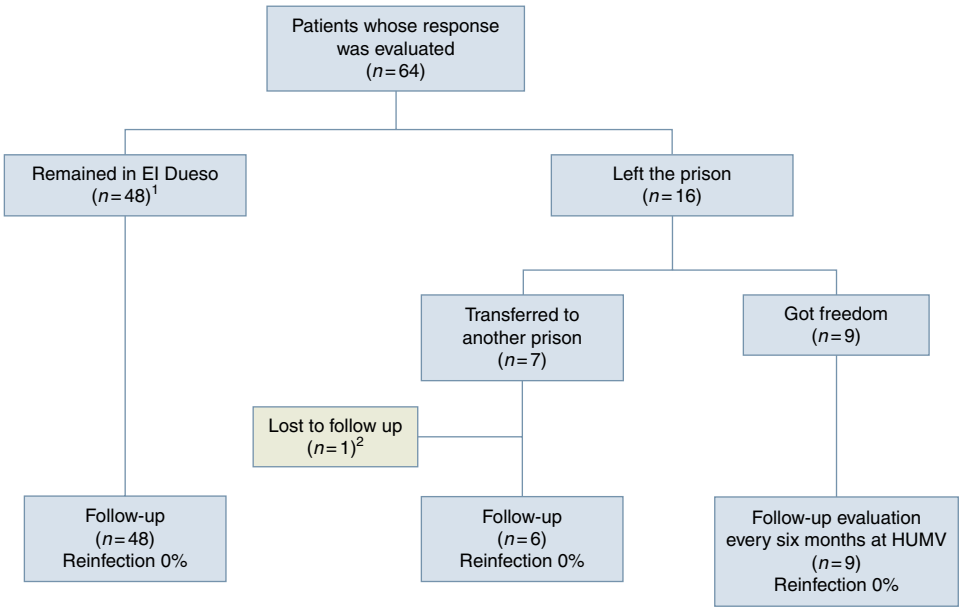

Fig. 5 Flow-chart of treated HCV prisoners whose response was evaluated and left the prison*. *Either after being transferred to another prison or after getting freedom; [1]Three genotype 3 patients had a virological breakthrough after the scheduled (sofosbuvir and ledipasvir) regimen but were successfully rescued with a 12-week length salvage regimen (sofosbuvir, elbasvir/grazoprevir and ribavirin); [2]One participant who got freedom (no follow-up data available). *HUMV* Hospital Universitario Marqués de Valdecilla

3.7/3.4 g/dL respectively. In both cases a SVR was obtained. No other serious adverse events were notified and no patient had to withdraw the treatment due to intolerance.

Primary outcomes

At the end of the observational period there were 409 inmates in El Dueso. At this point, no inmate had detectable HCV-RNA, which represents a prevalence of 0% (0.0–0.9%).

Similarly, there were no new cases of HCV infection during follow-up. Thus, a negligible incidence equivalent to 0 per 100 person-years could be estimated in this period. As a comparison, in 2015 the incidence of new cases of HCV infection had been 1.7 per 100 person-years.

By the time of this writing, 16 out of 64 treated patients whose response was evaluated during the study have left prison (nine of them reached freedom and seven were transferred to other penitentiary centers) (Fig. 5). Among them, 15 (93.8%) have had a scheduled follow-up without evidence of reinfection whereas one patient has lost follow-up (he was transferred to another prison, got freedom and lives in other Spanish region). At the moment, the median time that elapsed from the evaluation of the response to the last viremia determination is 12 months (5.5–14).

To sum up, as a whole there were only three relapses that were successfully rescued with a salvage regimen; neither, new (de novo) infections nor reinfections were recorded throughout the study period.

Evaluation of telemedicine satisfaction

All treated patients ($n = 66$; 100%) experienced teleconsultations and answered the satisfaction questionnaire (Table 1). The mode score was 5 (range: 1–5) with a mean score of 4.5 points (SD = 0.2).

DISCUSSION

This study was intended to eliminate chronic HCV infection in a Spanish prison through implementing a systematic "test and treat" strategy with DAAs. Under this approach, 14 months after the beginning of the program the HCV-viremia prevalence dropped from 10 to 0% and the incidence of new cases of HCV infection also dropped from 1.7 per 100 person-years to 0 per 100 person-years. These successful outcomes seem to be related to a high efficacy of the treatment (96.9% of SVR by ITT) and high adherence to the program (>99%). The implementation of telemedicine as a support tool showed a great acceptance rate among inmates. As far as we know, this is the first sustained program of systematic "test and treat" with DAA against HCV that has virtually eliminated the hepatitis C viremia in a prison.

Although the management of penitenciary healthcare has improved considerably throughout recent years, it still faces barriers that limit the goal of achieving an equitable and non-discriminative health care access for inmates. As a reflection of this situation, in the El Dueso prison in the previous 5 years only 53 antiviral treatments were administered and all of them were based on the administration of Peg-interferon and ribavirin. The implementation in prisons of a program of eradication of HCV based on interferon-free DAA-based regimens searches the former goal and also adds to the benefit of treating addictions and the intrinsic role of social rehabilitation of prisons. Thus, imprisonment can provide a unique opportunity to improve the health of these

individuals [9, 18]. In addition to the beneficial effects at an individual level, HCV elimination in prisons would generate relevant benefits for public healthcare [4]. Indeed, it is well known the persistence of high-risk behaviors both indoor and after release from incarceration (especially among people with substance use disorders), favouring HCV infection and transmission inside and ouside prison [19]. Although our program only proved its success in preventing new incident cases of HCV infection during incarceration, it can be expected a lower infective capacity from the ex-convicts towards the community after release. A rehabilitation program that includes specific measures addressed to drug addictions (i.e. talks, individual consultations, voluntary group sessions, psychological support, drug detoxification and a Needle-Exchange Program), and sexual risk behaviors, has been incorporated in El Dueso and could help to prevent reinfections. In fact, it could be speculated that spreading this strategy to other prisons could entail individual and public health benefits in the near future, but also opportunities for equity and health [4, 9, 18, 20].

Certainly, budgetary considerations need to be taken into account in order to direct monetary resources towards the most cost-effective health actions. An agent-based simulation cost-effectiveness model [treatment as prevention of HCV (TapHCV)] [21] has recently been adapted to the Spanish prisons [22]. This simulation considered HCV transmission, HCV prevalence, natural history of HCV progression, screening for HCV, and treatment with oral DAAs (at an average cost per treatment of €8055). The study concluded that prioritizing inmates by their health state is the most cost-effective strategy, resulting in an ICER of €9162 per QALY (using the commonly accepted willingness-to-pay threshold of €24,000 in Spain). However, a sensitivity analysis showed that even treating all HCV-infected inmates would further reduce the HCV burden and is cost-effective, with the ICER of €21,750 per QALY. Similarly, two recent mathematical models performed in the UK and the USA have demonstrated that universal opt-out HCV screening is cost-effective, particularly, if short-course IFN-free DAAs were used and IDU treatment rates were increased [21, 23]. Previous experiences have demonstrated that HCV treatment in incarcerated populations is feasible and meets the standard criteria for cost-effectiveness [12, 24]. A recent report describes the experience in three major Italian prisons of a program of test and treat chronic HCV inmates with DAAs only for those with advanced disease (F3–F4) according to Italian guidelines [7]. The "El Dueso" experience goes further in terms of extending treatments to all fibrosis stages, universal use of DAAs, and sustainability of the program over time, intending to become a real HCV-reservoir elimination program. Australian institutions are also developing interventional programs of screening and treatment in prisons [9].

Telemedicine technologies are being integrated into health systems, which can help improve access to specialty care in isolated populations. Proof of this was the ECHO project in New Mexico, an educational intervention designed to transfer subspecialty knowledge about HCV to primary care providers, thereby increasing patient access to HCV care [25]. Telecare has also showed effectiveness in the management of HCV-infected patients [26]. The use of telemedicine in this project has sought to eliminate barriers in the management of a vulnerable population (i.e. improving communication between health professionals, facilitating the inmate's access to the specialist, preserving their privacy and avoiding painful stigmatizing transfers). The selection of this form of consultation by inmates in the early phases of the study design and, subsequently, its high degree of satisfaction support its usefulness in settings such as prisons.

Clinical research in prisoners or other people whose liberty is restricted has been controversial from an ethical point of view. However, experts encourage it with the overall goal of permitting scientifically rigorous research to the extent it confers significant benefit without undue risk and in accordance with the prisoner's wishes and the recognition of their autonomy [27]. This low-grade interventional study fulfilled these premises, assured both a good level of prisoner involvement even in the design of the study, and a strict IRB monitorization of the study conduction. In other words, the individual rights prevailed over the general interest of the investigation.

Our study has some limitations. First, the exportability of the Jailfree-C experience to other areas and countries might be hampered if its conditions are not met (i.e. low-medium inmate population, telemedicine support, commitment of public institutions). In this sense, the recent SNSPHC approved in 2015 consider prisons as high priority centers of actuation [13] and cover its treatment for the next 3 years. Moreover, a program like the one described here may be more complex in other closed settings with a higher "turnover" of patients (i.e. jails, pre-trial detention centers, addiction centers, etc.). Likely, each of this kind of environment needs a specific micro-elimination policy directed to its special idiosyncrasy. Second, the full implementation of the program might be limited by patients that escape from the program when they are transferred to other centers. This limitation most certainly did not happen in the El Dueso prison, since these cases were few and consisted of patients whose stay in the center was expected to be less than 30 days. Finally, it could be speculated that some patients could have received a suboptimal regimen, particularly those with HCV genotype 3. However, the regimen was selected according to the Spanish guidelines in force at the beginning of the study, and the overall efficacy of the regimen was very high in genotype 3 patients (89.3% per ITT) as recently reported [28]. Moreover, all virological failures were adequately rescued with salvage therapies. At the time of this writing, the program is on going and all inmates continue to receive a personalized IFN-free treatment according to the current European guidelines and most of prisoners are currently treated with pan-genotypic regimens (mainly sofosbuvir+veltapasvir) [29].

In conclusion, this experience adds evidence on the benefits of running systematic HCV "test and treat" programs in prisons in the era of new DAAs by creating well-coordinated networks. This pioneer program is feasible and economic, and political efforts should be made to spread this initiative to obtain a true public health impact.

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CONFLICT OF INTEREST

Guarantor of the article: J. Crespo is the lead author and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. He confirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Specific author contributions: All authors had access to the study data and critically reviewed, revised, and approved the final manuscript. AC and JC designed the protocol, data collection tools, monitored data collection for the whole trial, wrote the statistical analysis plan, cleaned and analyzed the data, and drafted and revised the paper. They coordinated the study and initiated the collaborative project. They are the guarantors of the paper. SL, JC, J-IF and SA, analyzed the data, were in charge of the participant follow-up using telemedicine, performed FibroScan®, and drafted and revised the paper. SE was the infectious disease specialist in charge of monitoring co-infected patients; he participated in data collection and drafted and revised the paper. CC, J-RP and MM participated in data collection, coordinated the study in the prison, directed and supervised the telemedicine program and drafted and revised the paper. RP and JC performed the ultrasound studies and drafted and revised the paper. RA, ES and BC-F analyzed the data, were in charge of the psychological evaluation and care of the inmates and drafted and revised the paper. ML-H, JA, NC and FG were in charge of the analytical and microbiological part of the study and revised the draft paper; NC and FG performed the phylogenetic analysis. J-LC initiated the collaborative project, analyzed the data, and drafted and revised the paper.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Prisons are major reservoirs of hepatitis C virus (HCV).
- ✓ There is a substantial risk of HCV transmission during incarceration.
- ✓ HCV treatment in prisons faces different challenges that so far have prevented its universal implementation.

WHAT IS NEW HERE

- ✓ A sustained and universal "test and treat" strategy in a prison led to the eradication of HCV.
- ✓ It also prevented new incident cases of HCV (i.e. intra-prison transmission).
- ✓ The use of telemedicine favored the implementation of this strategy.
- ✓ Eradication of HCV in prisons is feasible and beneficial. Spreading this strategy should entail a public health impact

LIVER

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