Title: HCV micro-elimination in two prisons in Milan, Italy: a model of care

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ABSTRACT

People in prison represent a high-risk population for HCV infection control. With the advent of new direct antiviral agents (DAAs) HCV micro-elimination in prison setting became a feasible strategy. We assessed the impact of an intervention for HCV testing and treatment in 2017 and 2018 in a jail (San Vittore,SV) and a prison for sentenced individuals (Opera,OP). A dedicated protocol was applied and implemented over the two years. We collected data on demographics, HCV testing and treatment on all inmates present on October 31st 2017 and 2018. In the two facilities there were 2,366 and 2,369 inmates in 2017 and 2018 respectively; the majority were men (95.6%; 96.4%) and Italians (57.0%; 61.9%) with a median age of 41 years. Prevalence of lifetime reported drug use remained high (46.5%; 44.2%). HCV screening coverage was 89% in both years, while HCV-RNA test coverage increased (90.6%; 99.0%). HCV sero-prevalence remained stable (10.1%; 9.2%). In 2017 among inmates with HCV chronic infection 90 (42.4%) individuals had started DAAs treatment and 106 (54.6%) in 2018; of whom 38 (17.9%) and 74 (38.1%) achieved the SVR. The viremic pool decreased significantly over time (SV,24.4%; 15.4%;OP, 16.1%;<1%). Among inmates with HCV-positive serology in 2018, 121 (81.0%) were never linked to care before incarceration. Our study showed how a targeted and well-implemented HCV test-and-treat intervention in prison was feasible and effective in achieving micro-elimination. Viral hepatitis elimination agenda may help drawing interest onto this neglected population and bringing prison health higher up in the global public health agenda.

Introduction

Following the advent of HCV direct-active antiviral (DAAs), in 2016 the World Health Organisation has set the goal to eliminate viral hepatitis as a public health threat by 2030. (1). Yet, the elimination remains a challenge due the scale, complexity and cost of the treatment. In order to overcome some of these challenges, the HCV micro-elimination approach has been advanced (2). Population groups with high burden of chronic HCV infection or at increased risk for acquiring the virus would need to be identified as priority targets, including certain patients groups (e.g. haemophilic, patients with advanced liver disease, HIV-positive people) as well as people in prison, people with current/previous history of drug use, selected migrant communities based on epidemiological context of country of origin and men who have sex with men (3).

In EU/EEA countries, the prevalence of HCV infection among people in prison is considerably higher than in the general population (4), ranging from 4.9% to 86.3% against a prevalence from 0.1% to 5.9% (4)(5). Such difference reflects the synergic effect of multiple and overlapping risk factors in the prison population (4)(6): people with a history of injecting drug use, psychiatric patients and other vulnerable populations who have often reduced access to healthcare are overrepresented in prison (7). It is estimated that 30% of incarcerated men and 51% of incarcerated women are affected by drug disorders (8), and as many as 80% of people who inject drugs (PWID) report at least one incarceration event (9)(10). Injecting drug use remains the main risk factor for HCV in Europe accounting for 78% of all cases with a known transmission route and HCV represents the most prevalent blood-borne viral infection among PWID with a sero-prevalence in excess of 50% in many countries, including Italy (64.3%) (13)(14)(11). According to recent estimates, PWID population in the EU/EEA is well over 1 million (12).

According to WHO and EU, screening for HCV, followed by appropriate treatment, should be offered to all people in prison upon entry and during stay, in respect of the principle of equivalence of care and of clinical independence of healthcare professionals (13)(14)(15); however, rates remain worldwide low and multiple barriers affect treatment coverage (16). These include limited number of clinicians in prison, need for specialist visit for the prescription, high mobility of prison population, lack of cooperation with local service to guarantee continuity of care after release, high cost of therapy (17). Screening and treatment represent also an important instrument of prevention: the risk of infection persists in prison, where high-risk behaviours often occur, such as unprotected sex intercourses and sharing of injecting material, razors or materials for tattooing (6)(15).

In Italy, in 2018 the prison system housed around 60,000 inmates, the majority of whom were males and about 25% had substance use disorders (18). The estimated prevalence of HCV is much higher than in community (19)(20)(21).

In two large prisons in Milan, an expanded HCV test and treatment was implemented since 2017, after the Italian Agency of Medicine Drugs granted universal access to DAAs for the treatment of HCV chronic infection irrespective of liver disease stage (22). We aim to assess the feasibility and effectiveness of such intervention in achieving microelimination over the period of two years.

Methods

Hepatitis C treatment and care

Setting. Two large prison facilities are located in the Milan administrative area in the North of Italy: detention centre San Vittore (SV) and prison of Opera (OPE). SV is a pre-trial centre with a capacity for 1,000 inmates, houses both males and females and admits individuals directly from the community, who are awaiting trial, or sentenced for minor crimes to less than 5 years in jail with 200-300 new admitted per month. OPE is a maximum-security prison for 1,300 inmates, only men. Prisoners are transferred to OPE

from jail or other prisons with a sentence of more than 5 years. It admits about 30 new inmates per month with a median stay of 647 days.

Both facilities have a blood sample collection room, radiological services, nursing and emergency medical care 24 hours per day, 7 days per week. Psychiatric and infectious disease specialists provide daily consultation services during working days. Drug addiction services are also available providing psychological support, drug detoxification with methadone and buprenorphine/naloxone, peer support and voluntary group sessions. All clinical services are provided by San Paolo University Hospital and coordinated by the Regional Department of Public Health which depends from the Ministry of Health.

Protocol for screening and treatment eligibility process. In 2014, when the first generation DAAs (telaprevir) became available, specialist hepathology/gastroenterology services were strengthened in prisons to reach and maintain high coverage of HCV screening among newly admitted prisoners and to fast-track HCV treatment with DAAs for eligible inmates.

Integrated HIV, HBV and HCV antibody testing was performed on venous blood with a turn-around time of 48 hours. From March 2017 onwards, prisoners opting-out screening on admission were counselled by Infectious Disease specialists and offered rapid oral test. The newly admitted could refuse the screening after the counselling. All positive oral tests were confirmed by HCV serology testing. In OPE all new inmates were counselled and offered testing within a month of transfer, if previous screening results were not available or older than 2 years old. Regular HCV testing catch-up campaigns were conducted to increase coverage targeting patients who had previously refused the test.

From 2017 onwards, all HCV viraemic individuals regardless of the stage of disease and co-morbidities became eligible for DAAs in Italy (22). To cope with the new demand, eligibility assessment was streamlined. All inmates with HCV antibodies underwent HCV-RNA and HCV genotype testing; to study the severity of the liver disease the APRI score was calculated and ultrasounds was also performed, while elastometry was used only in a subgroup of patients. Regular multidisciplinary case discussions were implemented to optimize treatment for HCV infected inmates with co-morbidities considering potential drug interactions and possible switching to safer regimens. Staff from the justice system was invited to attend these meetings to discuss judicial aspects that could hamper the treatment, like duration of sentence, possibility of transfer to other prisons or allocation to correctional regimes alternative to detention.

Information and education. OPE introduced specific informative sessions for newly admitted prisoners on risk of transmission of HCV and prevention, HCV diagnosis and treatment options, as well as more general information about infectious diseases and risk of transmission during detention, perception of risk and consequences on mental health. Training and sensitization sessions were also offered to the detention officers and non-medical staff at risk for infection at work.

Continuity of care. In 2014 a national database was introduced to monitor and guide prescription of DAAs. This facilitated also interface between correctional facilities, hospitals and prison pharmacies guaranteeing prompt supply and delivery of medications. In agreement with penitentiary system, inter-prison transfers of individuals on treatment were avoided when possible. In case of unexpected/early release, proper written referral to appropriate healthcare facilities in the community was arranged and patient adequately counselled. Collaboration with community harm reduction services was strengthened.

Definition of study outcomes

The following outcomes were considered:

- Screening coverage: number of screened inmates over total number of inmates.
- Sero-prevalence: inmates with HCV antibody + over total of screened inmates.
- RNA availability: availability of RNA test over inmates with HCV Ab +.
- Diagnosis of HCV: HCV antibody positivity and RNA positivity.

- Linkage to care: individuals with HCV diagnosis and started on eligibility process.
- Treatment completion: reached the end of planned course of therapy, regardless of whether attended for Sustained Virologic Response (SVR) check.
- SVR: undetectable HCV RNA at 12 weeks after the end of treatment (EOT).
- Relapse: HCV RNA negative at treatment completion, but subsequently HCV RNA positive at 12–24 weeks post-treatment completion.
- No response: HCV RNA detectable at EOT.

Study population and design

Two cross-sectional surveys based on chart reviews were performed in SV and OPE in 2017 and 2018. All data related the screening, test results and treatment were recorded both on paper and digital charts. These records were extracted on an Excel table to be analysed. All inmates who were present on 31st October 2017 and on 31st October 2018 in SV or OPE were included in the study. The following variables were collected: demographic data (sex, country of origin, pre-incarceration drug use, duration of detention), HCV testing offered, HCV virologic testing (HCV RNA and genotype), HBV or HIV co-morbidities, eligibility data. Pre-treatment fibrosis, previous treatment history, type of regimen (DAAs vs interferon-based regimens) and date of treatment initiation were recorded for inmates who initiated HCV treatment. For viraemic inmates who did not start treatment, reasons for ineligibility were reported. Data collection was closed on the 31st December of the respective year. Data were extracted and entered into an access database for analysis.

In the cross-sectional study conducted in 2018, the location where the treatment had been started (OPE/SV vs community vs other prison) was recorded in addition to other variables described. The access to healthcare system was analysed comparing the number of treatments started in community and in prison.

For 2018 additional clinical data (DAAs data) on individuals who were on treatment with DAAs were available. We matched the inmates included in the survey 2018 with a second database, in which data of all inmates who started DAAs treatment from 1st January 2015 to 31st December 2018 were recorded. In this database, the following variables were longitudinally collected: demographic data (sex, age, country of origin, previous use of drugs), comorbidities with HIV and HBV and other comorbidities, the date of treatment initiation, evaluation of liver disease, including METAVIR score, transaminase and count of platelets in order to calculate APRI score, other liver function tests and HCV RNA, at baseline, at week 4, 8 if requested for the therapy regimen, 12 and 24 were recorded. The outcome of therapy and the reason of drop out (if relevant) were also collected.

We linked these databases to evaluate the quality of care (time to treatment, cascade of treatment). We also investigated time to treatment, defined as time from admission in prison to the start of treatment, as an indicator for quality of care.

Statistical analysis

We compared participants' characteristics between OPE and SV by the likelihood ratio test from the univariable logistic regression models in both 2017 and 2018 cohorts. We applied univariable and multiple logistic regression models to assess in the 2018 cohort the associations of demographic and clinical characteristics with proportion of HCVAb tested over the total, positive over the tested and treated over the positive participants; for each predictor, crude and estimated marginal percentages from the multiple logistic regression model were reported by category. All statistical tests were two-sided with a significance level of .05. For all the analyses the statistical software R v.3.6.2 was used.

Ethical consideration

The survey was performed on request of Regional health authorities. Ministry of Justice approved the study and granted a waiver on informed consent. Data were collected in accordance with the national ethical standards. No specific consent was required since data were collected in anonymous and aggregate form. Any specific information regarding the scope of the study was given to the participants.

Results

Comparison 2017-2018 and impact on viremic pool

On 31st October 2017, 2,366 inmates were living in the two facilities, 2,369 in 2018. Demographic characteristics are described in detail in Table 1. In brief, the majority were men (95.4%; 96.4%) with a median age of 41 years (IQR: 32 – 51) and were Italian nationals (57%; 61.9%), with no significant difference between the two years. When comparing the two facilities OPE and SV, significant differences were observed in nationality and age distribution: in SV the population was significantly younger and originated mostly from foreign countries (Table 1). Notably, among foreign nationals, the most represented region of origin is North Africa (22.1% in 2017; 26.4% in 2018). Both in San Vittore and Opera, the Italians inmates increased significantly in 2018 (Table 1). Almost half of inmates reported previous or current use of drugs (any drug), slightly decreasing prevalence over time (46.5% vs 44.2%). Positivity rates for HIV and HBV were comparable over time and between the two prisons (HIV 3.3% in 2017, 2.7% in 2018; HBV 2.7%; 2.5%).

Screening for HCV was offered to all inmates, reaching a coverage rate of 89% in both years (the refuse rate was stable at 11%), while HCV-RNA test coverage increased over time (90.6%; 99.0%), significantly in SV (p<.001) HCV sero-prevalence was stable (212, 10.1%; 194, 9.2%). At data collection closure, 90 (42.4%) and 106 (54.6%) started DAAs treatment and 38 (17.9%) and 74 (38.1%) of them achieved the SVR, respectively in 2017 and 2018: in Opera the number of inmates who achieved the SVR was significantly higher in 2018 (32; 61; p<.001) (Figure 1). Considering last available viremia on 31st December, in 2017 41 inmates (19.3%) were still viremic, 16.1% in OP and 24.4% in SV; in 2018 13 inmates (6.7%) were still positive for HCV RNA, of which only one in OP (<1%), who was affected by a psychiatric condition and refused treatment (Data no shown).

Linkage to care in the population present at 31st October 2018

Among population present in prison on 31st October 2018, 149 had a history of HCV chronic disease and were considered in need of treatment; 121 (81.0%) received HCV diagnosis and were linked to HCV care in OPE and SV, while only 16 in community (Figure 2).

Longitudinal study to assess quality of care in the population present at 31st October 2018

Among inmates present on 31st October 2018, some differences were recorded in HCV screening coverage: lower coverage was observed among foreign nationals (p=.06), and higher coverage among PWID (p<.001).

Positive HCV serology was significantly associated with female gender (p <.001), Italian nationality (p=.02), age older than 40 years (p<.001), reported use of drugs (p=.001) and HIV positivity (p<.001) (Table 2).

Among individuals with a HCV chronic infection diagnosis, no difference in treatment coverage was recorded with respect to nationality, age or reported drug use.

All inmates with chronic HCV infection were assessed for eligibility (including ultrasounds, HCV genotyping and other biomarkers), proposed treatment and started DAAs within a 4-month median time (data no shown). Out of 194 inmates with positive serology and present in prison on 31st October 2018, for 192 HCV RNA was available, 102 resulted positive and started DAAs in prison. In this population, the genotype 1 was the most represented (50.0%) and the combination glecaprevir/pibrentasvir was the preferred regimen (48.0%) (Table 3). Liver fibrosis was assessed by elastography for 67 (65.7%) inmates: of these, 43 (64.2%)

had a mild liver disease, while 24 (35.8%) had an advanced stage of fibrosis (F3 – F4) (Table 3). The APRI score was available for 102 patients: most of inmates had a score < 1 (73.5%).

Detailed analysis of cascade of care for the 2018 patients cohort (Figure 3) revealed that, out of the 124 inmates (63.9%) viraemic at admission to prison, 106 (85.5%) were treated with DAAs, 74 reached SVR while 4 were still on treatment at data collection closure. Among these, 3 inmates started the DAAs treatment before incarceration and continue it in prison. Out of pool (10) of people in need of treatment, 7 patients were still undergoing eligibility process or waiting to start the therapy, 2 refused the treatment and one was taking amiodarone, that represents a contraindication for DAAs. 8 patients were treated successfully with interferon-based therapy during imprisonment in the pre-DAAs era.

Only 2 people on treatment were lost to follow up due to release and extradition, respectively. Inmates still viraemic at the end of data collection were 13.

4. Discussion

In order to achieve the global goal of HCV elimination, as set forward by the WHO, certain population groups with high burden of disease would need to be targeted and prioritised for adequate interventions (3) People in prison are certainly one of those, due to the increased risk of acquisition and high prevalence of disease that characterise this population (5)(23)(24).

In this context, our study showed how a targeted and well-implemented HCV test-and-treat intervention in prison was feasible and effective in achieving micro-elimination, in two large institutions in Italy. We assessed the impact of such intervention over the period of two years in a jail (SV), characterised by high turnover, and a prison for sentenced individuals (OP).

While the HCV test-and-treat intervention was implemented since 2015, the DAAs access restrictions changed over time, with nationwide universal access to all HCV chronic patients only granted from 2017 (25)(26), resulting in a rapid expansion of the number of patients “treatable” also in the two study prisons. The clinical protocol developed by the local multi-sectorial team of healthcare professionals has proven successful in addressing those needs, reaching over the two-year study period very high and stable level of testing and treatment uptake among people in prison, as shown by the continuum of care data. Such data provided a clear evidence of how an adapted and targeted approach may be very effective in delivering high quality specialised healthcare to vulnerable population groups, as advocated by the micro-elimination approach (2). The experience reported in our study could represent a model transferable to other prison settings in Italy and beyond.

In line with current European guidelines (15), universal screening at entrance was implemented routinely, with rapid oral test. Testing rates were steadily above 90%, suggesting a high level of uptake among newly incarcerated individuals. Notably, some significant differences were observed among the study population, with PWID more likely to be tested as compared to non-PWID. This may be at least partially explained by the fact that PWID represent a recognised risk group for HCV, and as such may be over-prioritised or may be offered multiple opportunities to test (27). Women were also more likely to be tested, although this difference that we observed in our data cannot be explained by the increased prevalence of drug use disorders among this group as compared to men in prison in the multivariate analysis (8)(28), but may be linked to health seeking behaviour differences between the groups. Some variation in testing uptake was observed among foreign nationals, who were less likely to have undergone testing as compared to Italian nationals. This may be explained by possible cultural or language barriers that may have negatively influenced uptake, although the difference was not significant in the adjusted analysis.

Interestingly, the proportion of individuals testing positive for HCV-Ab who received a RNA confirmatory test increased over time, significantly in SV, suggesting improving efficiency of the HCV diagnostic pathway over the study period.

HCV-Ab prevalence in the study population was 10.1%, with no significant variation over time. Such value is lower than previously reported in other Italian studies (29) but still higher than the general population estimate (5)(20). This may be the result of both the concentration of high-risk individuals in prison, especially drug users and PWID who can be infected before incarceration (7), and the increased risk of infection during the period in prison. Environmental factors, such as overcrowding and inadequate infrastructures, and individual factors, especially common high risk behaviours, including continuing intravenous drug use, tattooing and unprotected sex, can determine this additional risk [17,18](8).. among incarcerated PWID was in fact significantly higher, confirming previous observation (4). HCV burden among women was also elevated as compared to men. This gender difference can be attributed to the higher frequency of overlapping risk factors in this group, such as injecting-drug use, sex work, mental health conditions and violence (8). Gender has been reported as an independent predictor of HIV and/or hepatitis C risk among women who inject drugs in many studies (30): it is not due to biological factors but to socio-behavioural factors such as the inability to negotiate condom use and the involvement in sexual work (28).Finally, HIV infection was significantly associated with HCV positivity, highlighting the complexity of health needs of the incarcerated population, as reported also elsewhere (4)(31). On the contrary, prevalence of HBV chronic infection, if higher in comparison to general population (5), was not significantly associated with HCV infection. While we did not explore in details HBV epidemiological pattern in our study, differences in the risk of developing chronic hepatitis B at older ages and in the weight of common risk factors on infection acquisition and prevalence, including population demographic (e.g. country of origin) and coverage of HBV vaccination, may have played a role.

Our study demonstrated that DAA-based treatment for HCV chronic patients is feasible in prison settings. The removal of restrictions to treatment access in 2017 has prompted the rapid and sustained scale-up in the number of treated individuals in the study prisons. Our test-and-treat approach has resulted in elimination of HCV in OP by 2018 and near-elimination in SV over a two-year implementation period, an achievement likely to be maintained over time due to universal testing at entrance.

The persistence of a viremic pool of HCV-infected individuals in SV highlights one of the main structural barriers in providing care in prison settings: the high turn-over of detained individuals (17). While OP is a prison hosting mainly individuals serving long-term sentences, thus representing a more stable and older population, SV is a jail with higher turnover characterised by a younger and multi-ethnic population. In this latter context, the implementation of test-and-treat intervention may be hampered by complex and often unpredictable population dynamics, e.g. short sentences and early release, as well as their specific characteristics, e.g. language and cultural barriers, stigma, mental issues. The latest change in DAAs access requirement, dropping the need for liver elastography assessment (26), coupled with shorter treatment course availability, may contribute to further fast-tracking treatment initiation and increasing completion rate also among highly mobile prison population groups.

Yet, some additional barriers to test uptake and treatment initiation persist. When considering factors influencing treatment initiation, younger age was associated with lower treatment uptake. This may be linked to the fact that in our study population, and in the prison population at large, younger individuals were more frequently incarcerated in jail (i.e. SV). While length of the incarceration period (lower in SV vs OP) may have had an impact on the feasibility of initiating and completing the eligibility process, individual attitudes towards clinical care and treatment and health-seeking behaviour may have played a role(32).

From a public health stance, our approach has the intrinsic added value of addressing and responding to the health needs of those population groups who are mostly deprived and less inclined to access specialized services when in the community (33). In particular, fast-tracking treatment for people in prison could be an effective strategy to address the larger and less easily identifiable population of PWID. According to our records, 80% of individuals linked to appropriate HCV care through our programme had no previous treatment experience, an observation in line with other similar fast-track treatment interventions conducted in Australia (34). In this perspective, providing high quality prison healthcare could be framed as an opportunity to advance the overarching goal of equitable access to healthcare.

The community dividend of effective prison health interventions targeting hard to reach population groups has been already demonstrated for hepatitis B in Scotland, where prison-based universal vaccination led to a significant increase in HBV vaccine coverage among community PWID (35) and has been already modelled for HCV (36). Indeed, PWID represent the main target population for HCV elimination efforts in Europe: the injective drug use account for 78% of all cases with a known transmission route (37). In our study 79% of people with HCV positive antibodies are current or previous injectors. Mathematical modelling suggests that globally, if the increased risk for HCV transmission among people who inject drugs were removed, an estimated 43% of new HCV infections could be prevented from 2018 to 2030 (38). Hence, while HCV treatment should be provided within a comprehensive basket of prevention services, *in primis* harm reduction services (39)(36), fast-tracking people in prison could be an effective strategy to address the larger and less easily accessible population of PWID.

The study presents some limitations. Linkage to post-release care remains a key issue to ensure adequate follow-up of patients, provide relevant harm reduction services (among other), and minimise the risk of HCV re-infection for those at continuous risk (17)(40). In our study, active referral to specialised healthcare services in the community was implemented for individuals in need. Unfortunately, we could not assess the extent to which diagnosed or treated patients were successfully linked to appropriate care after release.

Other limitations may have affected our analysis. We used routinely collected data sourced from patients' records, and we could not check their accuracy. Due to possible overlapping in the population, it is possible that the same individuals are present in both the 2017 and 2018 data sets; as the data were anonymized, we could not take this into account in the analyses. Due to the nature of our study design, some variables (e.g. eligibility assessment, treatment, treatment outcome) were only available for a subset of patients. Moreover, not all study participants have been tested, with possible unpredictable effect on the estimates.

In conclusion, we reported how targeted and locally adapted HCV test-and-treat intervention may be successful in rapidly achieving micro-elimination in prison. While viral hepatitis elimination program may require intensified efforts to address prisoners' needs, it may as well be a beacon to draw interest onto this neglected population and help bringing prison health higher up in the global public health agenda.

Declaration of interest/Funding

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No additional funding was required for the design and conduct of this study.

Authors' contributions

RG, TS, RR, VC and LT contributed to the conception and design of the study. RG, TS, EF and RR were responsible of all clinical procedures and acquisition of data. VC, GA, GS, LT, MF and LB performed the data analysis. All authors contributed to interpretation of data. VC and LT drafted the first version of the manuscript. All authors contributed to manuscript drafting and approved the final version.

Potential conflicts of interest

The authors have no conflict of interests to declare.

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