



## Liver, Pancreas and Biliary Tract

## Milestones to reach Hepatitis C Virus (HCV) elimination in Italy: From free-of-charge screening to regional roadmaps for an HCV-free nation



Loreta A. Kondili<sup>a,\*</sup>, Alessio Aghemo<sup>b</sup>, Massimo Andreoni<sup>c</sup>, Massimo Galli<sup>d</sup>,  
Alessandro Rossi<sup>e</sup>, Sergio Babudieri<sup>f</sup>, Felice Nava<sup>g</sup>, Claudio Leonardi<sup>h</sup>,  
Francesco Saverio Mennini<sup>i</sup>, Ivan Gardini<sup>j</sup>, Francesco Paolo Russo<sup>k</sup>

<sup>a</sup> Center for Global Health, Istituto Superiore di Sanità, Viale Regina Elena 299-00161 Rome, Italy

<sup>b</sup> Humanitas University and Humanitas Clinical and Research Center IRCCS, Rozzano, Milan, Italy; Secretary of Associazione Italiana per lo Studio del Fegato (AISF), Italy

<sup>c</sup> Department of Systems Medicine, University of Rome "Tor Vergata"; Infectious Diseases Clinic, University Hospital "Tor Vergata", Rome, Italy. Scientific Director of Società Italiana di Malattie Infettive e Tropicali (SIMIT), Italy

<sup>d</sup> Department of Biomedical and Clinical Sciences "Luigi Sacco", University of Milan, and III Division of Infectious Diseases Luigi Sacco Hospital, Milan, Italy. Past president of Società Italiana di Malattie Infettive e Tropicali (SIMIT), Italy

<sup>e</sup> Società Italiana di Medicina Generale e delle Cure Primarie (SIMG), Italy

<sup>f</sup> Department of Medical, Surgical and Experimental Sciences, Infectious and Tropical Disease Unit, University of Sassari, Italy; Società Italiana Medicina di Sanità Penitenziaria (SIMSPe), Italy

<sup>g</sup> Scientific Director Federazione Italiana degli Operatori dei Dipartimenti e dei Servizi delle Dipendenze (FeDerSerD), Italy

<sup>h</sup> President of Società Italiana delle Patologie da Dipendenza (SiPaD), Italy

<sup>i</sup> Economic Evaluation and HTA (EEHTA), CEIS, Faculty of Economics, University of Rome "Tor Vergata" and Institute of Leadership and Management in Health, Kingston Business School, Kingston University, London, UK. President of Società Italiana di Health Technology Assessment (SiHTA), Italy

<sup>j</sup> President of Patients Association EpaC, Italy

<sup>k</sup> Department of Surgical, Oncological and Gastroenterological Sciences, Gastroenterology Unit, University of Padua, Padua, Italy. Italy Co-ordinating Committee of Associazione Italiana Studio Fegato (AISF), Italy

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## ABSTRACT

Although Italy has been on track for Hepatitis C Virus (HCV) elimination since 2019, it fell off track due to the decrease in the number of treated patients. HCV elimination in Italy will be possible if immediate action is taken. A health policy was implemented beginning in 2021, consisting of screening among key populations and birth cohorts (1969–1989), estimated to have a high prevalence of undiagnosed individuals. The active screening requires regional governance that manages the processes' complexity integrating a well-organized network between territory assistance and hospital to achieve an effective HCV care cascade. This document aims to support the regional decision-making process by defining paths for screening and linkage-to-care. Implementing active screening strategies beyond a risk-based approach is required as a General Practitioners' task. Simplified paths must be drawn for the key populations screening. The infrastructure built for COVID-19 vaccination could be used also for HCV screening. According to a multidisciplinary care delivery, screening should be supplemented with rapid linkage-to-care and treatment of newly diagnosed patients. The realization of the proactive screening during the first two years is vital because it will define the tracks for the whole HCV cost-effective screening of 1948–1988 birth cohorts in Italy.

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## 1. Achievements in the policy-making process for the HCV elimination in Italy

Viral hepatitis is an important public health problem that affects about 71 million people worldwide, spreading as a silent epidemic. A life without Hepatitis C virus (HCV) is achievable since the availability of direct-acting antiviral drugs (DAAs). Viral hepatitis elimination signed up to 17 Sustainable Development Goals

\* Corresponding author.

E-mail address: [loreta.kondili@iss.it](mailto:loreta.kondili@iss.it) (L.A. Kondili).

as a focus area in the health-related goals. In response, World Health Organization (WHO) drafted the Global Viral Hepatitis Strategy, adopted in 2016 by all Member States. This Strategy carried ambitious targets, and stakeholders from each country are compelled to define Nation Hepatitis Plan, including specific roadmaps to achieve WHO elimination goals [1].

Italy witnessed the highest number of HCV liver-related deaths in the past and the highest number of treated patients with DAAs since their first approval in Europe [2]. Due to the extensive rollout in treatment since 2015, the 65% reduction in liver-related death is forecasted in Italy by 2022–2025 [3]. In 2017, Universal access to antiviral treatment for chronic HCV infection was available as part of the Italian HCV elimination national plan due to dedicated funds toward innovative non-oncological drugs. This guaranteed the release of DAAs to all diagnosed patients with HCV chronic infection without any budget restriction [2]. It was also possible to extensively treat transfusion-dependent thalassemia patients, patients with chronic kidney disease on dialysis, and children born by HCV infected mothers, populations strongly associated with risk factors for HCV infection. This health policy guaranteed HCV confinement in these high prevalence groups, emphasizing that HCV “micro-elimination” alleviates the burden of nationwide screening efforts supporting the roadmaps toward elimination. Following this achievement, Italy was listed as a country on track to achieve the WHO’s elimination goal in 2018 [4]. However, the pool of diagnosed patients is estimated to run out before 2025, leaving a high infection burden without diagnosis and treatment [3]. The decrease in treatment rate in 2019 and almost an interruption of antiviral treatment during the COVID-19 pandemic is a source of great concern [5]. According to a survey by the Italian Association for the Study of the Liver (AISF), a drastic decrease and suspension of outpatient visits and prescription of antiviral treatment even for patients with compensated cirrhosis, at high risk of disease progression and development of complications, was observed nationwide [6]. Based on the decreased treated patient since 2019, Italy has fallen behind in achieving the WHO elimination targets [7]. In Italy, among people awaiting treatment and diagnosis by screening, about 100,000 may have advanced liver fibrosis [8]. It is estimated that delaying treatment with DAAs for six months in Italy (due to the COVID-19 pandemic) will determine over 500 deaths from HCV-related liver disease after five years [9]. Immediate restoration of testing and treatment could avoid this increased mortality and translate the DAA efficacy into population-level effectiveness. Currently, HCV therapy’s limitation is no longer treatment efficacy or adherence but the identification of available patients to treat [10–13]. A close relationship between the scientific world and the stakeholders will help to arrange cost-effective HCV screening strategies and achieve the WHO elimination target.

Previous studies reported that HCV treatment during 2015–2019 brought important medium to long-term health and economic benefits for Italian National Health System (NHS) in terms of cost-saving from the avoided clinical events (HCC development, decompensated cirrhosis, and need for liver transplantation). The initial investment in antiviral treatment was estimated to be recovered by approximately 5.5 years (95% CI: 3.75–6.08) [14,15]. The Italian policymakers well-received this crucial scientific evidence as well as the cost-effective screening strategy regarding birth cohorts and key populations in Italy. An important political action was recently approved and an amendment to the Governative Milleprogrhe Decree allocated 71.5 million Euros for the years 2020–2021 to introduce a free-of-charge screening program as an experimental project with the final goal of identifying undiagnosed individuals with chronic HCV infection [16,17]. The HCV free-of-charge screening will focus on the key populations (current intravenous drug users) in the public services for drug addiction (SerD), peo-

ple detained in prison, and cohorts of the general population born between the years 1969–1989 [17].

## 2. Implementation of the HCV elimination plan requires new development paradigms of health systems

The implementation of the proactive screening in birth cohorts and key populations requires focusing on the present organizational problems. Italy is divided into twenty regions with their broad discretion in planning, organizing, and financing health care services within their territory, while the State is limited to formulating general principles. Although in Italy a National Hepatitis Plan exists, it has not been funded and implemented. In addition, decentralized HCV care models persist with no uniform strategies across regional networks. Only a few regions throughout Italy have developed adequate organizational and operational politics regarding HCV elimination. Linkage-to-care is limited, and enhanced HCV screening and diagnosis is not implemented in the country. The number of prescribers is restricted only to gastrointestinal and infectious disease specialists, limited per region. Besides, no specific strategies for marginalized patients and at-risk groups are implemented at the national level. If screening adherence is not appropriately addressed, the WHO elimination goal is unlikely to be reached by identifying the ideal screening strategy alone [18].

It is of paramount importance to promote proactive screening according to specific roadmaps for each region, with the final goal of achieving the high effectiveness of this intervention nationwide. Thus, the role of scientific societies is crucial. This document aims to support the regional level’s decision-making process to define a unique path for screening and linkage-to-care. The realization of the proactive screening during the first two years could define the future tracks for the whole screening strategy (birth cohorts born between 1948 and 1988) reported as cost-effective in the Italian epidemiological context [16].

## 3. HCV screening in birth cohorts of general population involving the general practitioner (GP)

The General Practitioner’s duties include adherence to health care and prevention activities agreed at the regional level embedded with the most representative trade union organizations. These agreements provide for specific program implementation procedures and verification of the achievements regarding the objectives. HCV Screening based on the known risk factors has been indicated in a consensus paper of Italian Society of General Medicine and Primary Care (SIMG) and Italian Association for the Study of the Liver (AISF) [19]. However, it is not feasible and straightforward in all realities. In addition, several studies have shown that it is not always effective in discovering the undiagnosed infected population [20–23]. Implementing innovative active screening strategies beyond a risk-based approach is required to be fully applied as a GP task, as part of the WHO objective for eliminating hepatitis by 2030. Need for action is required at regional levels to contract the role of the GPs in the active free-of-charge HCV screening campaign for the 1969–1989 birth cohorts.

## 4. Recommendations

- The governance of the processes that serve to achieve the screening and the linkage-to-care must be well defined by the National Hepatitis Plan (PNEV) with specific indications defined for regional governments.
- As identified in the HCV screening law decree, specific actions should be implemented through dedicated regional plans. A dedicated Control Room in each region should define the strategic screening plan, manage the resources, coordinate the activities, collect, elaborate and transmit the outcome measures.

- Agreements between regional governments with GPs' trade unions are required to standardize the GP's role on the national territory and guarantee the equity of the access to care for HCV elimination.
- Each region's government must map the specialized public and private affiliated laboratories that will be reimbursed for HCV testing of the birth cohorts indicated by the HCV screening law (Milleproroghe Decree).
- The HCV screening should correspond to a specific code (exemption code) that each region would generate. This code should include the first level test (HCV-Antibodies) and, in case of positivity, the HCV RNA confirmation by reflex testing, to ensure a high adherence by simplified single-step screening
- The HCV opportunistic screening is indicated explicitly by the law decree and gives the possibility to request HCV screening tests in patients born between 1969 and 1989 and admitted to the hospital (as inpatients, outpatients or in the emergency departments). Once the regions have provided the specific HCV screening exemption code in the NHS booking system, HCV testing could be easily performed in all NHS structures.
- GPs and other specialists should evaluate any risk factor associated with HCV infection. This also includes other birth cohorts that are not covered by the free-of-charge screening in these two years, as suggested in the shared document proposed by GP and hepatologists regarding the management of a patient with chronic liver disease [19].
- An improvement of the communication between the two assistance networks, the territorial and the hospital, is the key element that could guarantee the equity of access to health care among all persons infected with HCV and an effective care cascade for HCV elimination.
- An interconnection of services that includes GPs, reference laboratories, and specialists could guarantee: 1) simple and quick path for the individuals eligible for free HCV screening; 2) rapid management, if active HCV infection is identified; 3) post-therapy follow-up at Specialized Centers, for patients with other cofactors for liver damage or comorbidities, and at GPs for the other patients that achieve viral eradication.
- It is necessary to intensify the commitment for training, information, and collaboration regarding the screening and the linkage-to-care activities between GPs and Specialists. They should be planned in a structured way to increase the GP's awareness, involving Italian Association for the Study of the Liver (AISF), Italian Society of Infectious and Tropical Diseases (SIMIT) and the Italian Society of General Medicine and Primary Care (SIMG).
- A web-based tool is required in each region for identifying those entitled to screening, connecting the steps from the screening prescription/conduction to treatment referral.
- Specialist visits through telemedicine could be a valuable tool for simplifying patient's treatment and follow-up, as long as it is made realistic, with traceable reservation, both for administrative and clinical purposes.
- Combining the SARS CoV-2 screening with the screening for HCV infection is desirable and has been successfully conducted in various Italian settings.
- COVID -19 vaccinations could be utilized in each region to increase the awareness and HCV screening rate for the birth cohorts and key populations.

## 5. Screening and treatment of key populations: an essential public health challenge

Innovative strategies are required to enhance screening and linkage-to-care for the so-called 'hard-to-reach' populations. People who inject drugs (PWID) and inmates are considered "key pop-

ulations" at risk of acquiring HCV infection. Diagnosis and treatment of HCV infection in these populations are crucial either to achieve HCV elimination targets or for public health. In epidemiological terms, diagnosis and treatment of HCV infection among the consumers of substances represent a priority for at least four reasons:

- (1) they represent the major reservoir and spreaders of the virus (a consumer of substances can infect within the first three years of infection at least 20 other consumers) [24]
- (2) drug users with chronic HCV infection have high morbidity and mortality due to limited access to treatment [25]
- (3) DAAs are very effective among substance users (sustained virological response > 95%) [26,27]
- (4) therapy aimed at eliminating the infection serves as a prevention method, lowering the circulation of the virus and its transmission, thereby new infections and reinfections [25,28].

The HCV prevalence among the population that uses substances varies between 30 and 60%. At least 90,000 HCV infected individuals among drug consumers are estimated to be referred to the services for drug addiction (SerDs) in Italy [29–31]. Epidemiological data have suggested that at least 150,000 actual or previous drug users have an undiagnosed HCV infection [29,8]. Despite being strongly recommended, HCV screening in PWID is still low, there are several difficulties for their referral and linkage-to-care, thus PWID populations have been systematically under-treated. [25].

The test for hepatitis C is available in all Italian prisons guaranteed by the Essential Level of Assistance (LEA); however, only a few prisoners manage to get tested. As with the SerDs, the most critical reasons limiting the systematic screening of inmates are logistical and organizational. Although prison is a concentrator of pathologies, there are several challenges in implementing clinical practice standards. Inmates do not have the state of health as a priority; thus, HCV screening and treatment, if oriented in a simple and rapid way, could accomplish HCV elimination easily during the prison staying rather than in their free status[32–34]. The prevalence of anti-HCV in Italian prison settings varies between 20 and 40% [35,36]. It is likely that in the Italian prisons, up to 30–35,000 anti-HCV+ subjects may transit each year [29]. Recently a 10% reduction in prevalence rate was observed, of which only 40% had an active HCV infection [37]. Intensive antiviral treatment in the recent year could explain the reduction in HCV prevalence in this population. Being a user of substances (PWID) is the main risk factor for HCV infection in prisons. National and international scientific societies strongly indicate a simplified path for HCV screening, linkage to care and treatment of key and marginalized populations [38–40].

In addition, sufficient healthcare needs to be provided, and tailored efforts must be made to reach otherwise neglected individuals such as Men who have sex with men, sex workers, homeless individuals. The low HCV testing and linkage-to-care rates remain an important gap also in migrants [41–43].

## 6. Recommendations

- HCV screening should be **offered to all drug/substance users** based on a person-center approach.
- The HCV screening law decree represents a great opportunity in that indicates the point-of-care as the only path for HCV elimination in key populations. The point-of-care guarantees a rapid process that starts from screening to therapy and counseling for harm reduction in the places where the patient is presented, i.e., SerD or the prison. The point-of-care is a horizontal organization that can and must satisfy the needs of users. In line with

the current Italian Drug Agency (AIFA) criteria for the DAA prescription, point-of-care also provides for three moments to be managed within the SerD and prison

- psycho-educational and motivational counseling and screening;
- specialist evaluation (a dedicated specialist outside the care point) and the start of therapy;
- follow-up during and after therapy.
- A people-centered approach and application of a test and treat model are highly recommended, wherever possible, to eliminate gaps between diagnosis and treatment.
- The HCV screening law decree allowed, as a further crucial step for the PWID population, the possibility to carry out the rapid HCV RNA testing, as a single and important step to speed up the treatment process. This step must be adequately conceived in all regions, guaranteeing this simplified screening for the PWIDs.
- It is essential that actions are rapidly conducted within the services. To further persuade a better relationship with patients and increase their awareness, the medical professionals of SerD and prisons should be actors of the whole process from screening to cure, ensuring continuity of treatment. Scientific societies (FeDerSerD, SiPaD, and SIMSPe) and patient's association (EpaC) are promoters of initiatives aimed at giving a greater role to doctors of SerDs and prisons to streamline the HCV screening and DAA therapy.
- **All patients eligible for treatment should be referred to the specialist** (infectious disease/ hepatologist) accompanied by **a motivational counseling**.
- It is desirable to develop a treatment plan that includes clinical assessment and biochemical liver disease staging within SerDs and prisons. The specialist could remotely (potentially through telemedicine) evaluate the patients' clinical data and indications for treatment reported by the doctor of prison or SerD, prescribe treatment and post-treatment monitoring plan, if necessary. This interdisciplinary, integrated organization among SerD and prison doctors, and specialists (hepatologists or infectiologists) could guarantee close monitoring of the compliance with the treatment, based on the therapeutic and the motivational support.
- The screening, **if refused or negative, should be re-proposed periodically, combined with motivational counseling**.
- Screening activities must always be accompanied by harm reduction actions. **All patients referred to a specialist** (infectious disease/hepatologist) for treatment should receive a **structured harm-reduction program** (knowledge of the principles and measures, as indicated by WHO)
- The harm reduction activities are not funded by the dedicated screening budget but are recognized in Italy as Essential Level of Assistance (LEA) for the PWIDs, since 2017. Scientific society's understanding of this LEA's actual application in each region is of fundamental importance to achieve the elimination targets. The implementation and expansion of harm reduction activities should be conducted in concert between scientific societies and health personnel operating in SerDs and prisons.
- For prisons, screening and treatment must be organized within the Regional Observatories for the Protection of Health in Prison, in most regions existing only on paper. The Regional Observatories for the Protection of Health in Prison must guarantee the collection of structured information on the effectiveness of the screening intervention required by the HCV screening law decree and evaluate the most effective steps to be taken for the next two years.
- AISF and SIMIT emphasize the need to implement specific micro-elimination programs in other at-risk populations, such as men who have sex with men (MSM) and sex workers not explicitly addressed in this screening law decree. Migrants should

also garner particular screening efforts, as they are the hardest group to track, especially when they are undocumented. Integrated screening for infectious disease (Tuberculosis, HBV, HIV and HCV) is recommended in these high risk populations.

- The surveillance of new infections in high-risk groups has not been addressed in the present HCV screening law decree. In populations with high-risk factors, such as drug users, MSM, sex workers, the control of new infections and post-treatment reinfection should be part of the Essential Levels of Assistance. HCV screening every six months should be conducted, according to the specific regional indications for these key populations.

## 7. Screening to complete the cascade of care and achieve HCV elimination

Elimination of viral hepatitis by 2030 is an ambitious but achievable goal. Achievement of elimination will depend on technical capabilities and leadership, political will, and financial considerations. Even with strong leadership and political will, availability of finances, the application of funds, and health system capabilities will determine the magnitude and response speed [42]. Screening alone is insufficient for Italy to achieve the WHO's HCV elimination target. A commitment is needed by the State to fully support the WHO elimination goals for chronic HCV infection, which remains a silent public health threat.

Reaching the Screening/Diagnosis should be considered only the starting milestone. The screening efficiency must be matched by a rapid linkage-to-care and cure of patients with HCV infection. The Italian evidence regarding the cost-effectiveness profile of HCV screening and DAA treatment produced from the Italian NHS perspective supports an evidence-based health policy for HCV elimination in Italy[14–16]. The evidence on cost benefits of treating patients diagnosed by screening is important for the ongoing central and regional decision-making process. In a recent evaluation of the centre for Economic and International Studies of the University of Tor Vergata and Istituto Superiore di Sanità, the investment in treating newly diagnosed patients was translated into a significant reduction of liver disease complications with great economic benefits. For 1000 standardized treated patients diagnosed through the active HCV screening, 660 irreversible liver damage avoided are estimated, accruing €65.22 million net savings for the Italian NHS over a 20-year time horizon. The initial investment in treatment will be recouped in 4.4 years, in the form of savings from the disease complications avoided. This action can reduce the infection rate and clinical and economic disease burden of HCV infection in Italy.

Considering that more than 20% of treated patients in 2019 had cirrhosis or advanced liver fibrosis and a similar prevalence of the advanced disease has also been estimated for undiagnosed individuals, DAAs should be considered life-saving drugs [2,8]. Additionally, several studies have shown that HCV-related disease inflicts an enormous economic and clinical burden due to HCV-related extrahepatic comorbidities. Early eradication of HCV could reduce these burdens [14,44,45]. However, providing HCV treatment to diagnosed individuals could be a challenge. The dedicated fund of the Italian State for "Innovative- Non Oncological- Drugs", which provided the necessary budget for DAAs, expired in April 2020. Thus, all Italian regions, lacking the regional plans for HCV elimination, will face the challenge of finding a way to pay for the DAAs. Although the new HCV screening policies address key points for HCV elimination, the lack of a dedicated fund for DAAs would stress an already overburdened regional budget. In most regions, in the absence of regional elimination plans, the treatment curve will drastically decrease, and Italy will move further away from achieving the HCV elimination targets [7]. According to a multidis-



ciplinary delivery of care, screening should be supplemented with rapid linkage-to-care and treatment of newly diagnosed patients in order to avoid the disease progression risk and ethical issues related to a decreased quality of life due to untreated viral infection.

## 8. Recommendations

- The financial commitment to strive for the screening strategy and treatment to eliminate hepatitis C must be considered an investment rather than a cost.
- An active screening campaign could be considered as a starting point. An effective screening should be supplemented with a rapid linkage-to-care and treatment of the newly diagnosed patients.
- Establishing an *ad hoc* fund for the DAA treatment for each Italian region binding resources both for case finding by active screening and treatment, within the National Plan for the Prevention and Treatment of Hepatitis C is of paramount importance to keep Italy on track to achieve the WHO elimination targets by 2030.
- The investment of 71.5 million euros concerns only the first part of the recommended graduated screening. Therefore, a further investment must be guaranteed for the remaining population to conduct an active screening of the entire cohort of individuals born between 1948 and 1988, estimated to have a high prevalence of HCV infection, yet to be diagnosed [16].
- Together with scientific organizations, regional stakeholders have to develop micro-elimination strategies in key populations other than those indicated in the HCV screening law decree to move toward HCV elimination in each Italian region.
- Finally, the measurement of the effectiveness indicators of screening and linkage-to-care required by the HCV screening law decree for each region is of fundamental importance to provide evidences on the size of the yet undiagnosed population and on actions and health policies necessary to achieve the HCV elimination targets.

## Conclusions

- A close interaction between the scientific and institutional world is required at a national, regional, and local level to discover the undiagnosed individuals with active chronic HCV infection. The active offer of screening is an important milestone that requires regional governance that manages the processes' complexity integrating well-organized interdisciplinary paths between territorial and hospital specialized medicine. Each region must identify the objectives and strategies to define the present and future steps and reach HCV elimination goal by 2030. The State, continuing its efforts to make the health system more sustainable, must strengthen its role in addressing and verifying regional health systems to guarantee the equity of care for all citizens. Investing in the immediate DAA treatment of individuals with active infection means improving health and having an economic return for NHS in the short to medium term. The infrastructure built for COVID-19 vaccination, could be successfully used by each region for HCV screening of birth cohorts and key populations, as part of a micro elimination approach in the lasts. Following the first two years of screening, new investments are required to cover screening for the entire cohort of individuals born between 1948 and 1988 to achieve the WHO elimination targets by 2030.

## Declaration of Competing Interest

On the behalf of all authors declare no conflict of interests for the present paper

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