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COMMENTARY

Challenges on the achievement of World Health Organization goals for HCV elimination in Italy: need for a Regional programmatic approach on screening and linkage to care

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Abstract
Italy has been one of the countries with the greatest burden of HCV in Western Europe and with the highest number of HCV liver-related deaths. In order to achieve HCV elimination by 2030 Italy, like many other countries, will need to succeed in tackling the undiagnosed individuals with active HCV infection. To this aim beginning in 2021, a nationwide action has been implemented, consisting of the performance of screening tests among key populations and birth cohorts (1969-1989), estimated to have a high prevalence of undiagnosed individuals. The realization of the proactive screening during the first two years will define the tracks for the whole optimized screening strategy, including also the screening of 1948-1968 birth cohorts, reported to be the best cost-effective strategy in achieving the HCV elimination targets by 2030 in Italy. Each Italian region needs to define the present and future steps to reach HCV elimination goal by 2030 guaranteeing the equity of care.

Key words
- hepatitis C
- infection
- WHO elimination goal

In 2015 Viral Hepatitis C (HCV) infection was acknowledged as a global health and development priority signed up to 17 Sustainable Development Goals. Viral hepatitis was included as a focus area in the health related goal – Goal 3.3. In response, the World Health Organisation (WHO) drafted the Global Viral Hepatitis Strategy which was then subsequently adopted in 2016 by all Member States. The world leaders will be pledging to "combat" viral hepatitis infection as a global health threat through ambitious targets which if reached will reduce the number of deaths by 65% and increase treatment rates up to 80% by the year 2030 [1]. Stakeholders from each country are compelled to define Nation Hepatitis Plan, including specific roadmaps to achieve the WHO elimination goals for chronic HCV infection.

Italy has been one of the countries with the greatest burden of HCV in Western Europe and with the highest number of HCV liver-related deaths [2, 3]. Thanks to health policies that permitted the universal use of direct acting antiviral drugs (DAAs) for all HCV diagnosed patients, using a dedicated fund for innovative non-oncological drugs, since 2017 Italy has been on track for HCV elimination. However, recent evaluations have reported that due to the declined number of the treated patients, starting since 2019 and continuing during the year 2020-2021, due to the COVID-19 pandemic [4, 5], Italy will not be able to achieve the HCV elimination goals. Up to now, more than 220,000 patients have been treated with DAAs, the remaining are estimated at least 280,000 individuals unaware of their HCV active infection [2, 6]. HCV elimination in Italy will be possible if immediate action is taken now. Italy has drafted a National Hepatitis Plan and the State, continuing its

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efforts to make the health system more sustainable, needs to strengthen its role in addressing and verifying regional health systems to guarantee the equity of care based on guiding principle that no one will be left behind. Italy is divided into twenty regions and under the Italian Constitution, each region is an autonomous entity with defined powers. Based on broad discretion in planning, organizing, and financing health care services within their territory each region needs to identify the objectives and strategies to define the present and future steps to reach HCV elimination goal by 2030. In particular, the regional roadmaps to HCV elimination need to address the following key points.

- In order to achieve HCV elimination by 2030 Italy, like many other countries, will need to succeed in tackling the undiagnosed individuals with active HCV infection. To this aim beginning in 2021, a nationwide action has been implemented, consisting of the performance of screening tests among key populations and birth cohorts (1969-1989), estimated to have a high prevalence of undiagnosed individuals [7, 8]. The active screening offer requires a regional governance that manages the complexity of the processes integrating a well-organized network between territory assistance and hospital with the goal of an effective HCV care cascade. The realization of the proactive screening during the first two years is important because it will define the tracks for the whole optimized screening strategy, including also the screening of 1948-1968 birth cohorts, reported to be the best cost-effective strategy in achieving in Italy the HCV elimination targets by 2030 [8].
- Emphasis will need to shift from treatment of diagnosed patients to screening of infected, but undiagnosed individuals according to optimized diagnostic and care pathways. A substantial loss of patients between each step from diagnosis to cure of infection has been observed in different populations [9, 10]. In the context of scarce healthcare resources, information on impact and real-world affordability of different diagnostic pathways, that guarantee substantial increases in diagnoses for entry into the treatment cascade is crucial. The traditional diagnostic algorithm approach is based on HCV Antibody (HCV-Ab) and HCV Ribonucleic Acid (RNA) assays which both have very high sensitivity and specificity, making false-positive and false-negative results rare occurrences. However, this traditional approach, that include several steps in the diagnostic process, often lead to incomplete diagnosis and miss of cure opportunity. Simple rapid test using saliva or capillary test have been widely used to detect the presence of HCVAb with particular regard in key populations and has shown to reduce time between the initial observation and treatment administration [11]. However the real challenge of the traditional or rapid antibody detection approaches is the need for two or more steps for the diagnosis of active infection which has been shown to complicate the patient journey and as consequence to increase the number of patients lost before receiving treatment. The cheap price of HCV Ab capillary tests is an attractive option for Regional stakeholders. However, this approach, though attractive for outreach first step of screening for special populations, subsequently requires referral for conventional phlebotomy confirmation of active infection and was the less cost-effective option out of different screening pathways analysed. Based on cost effectiveness data in the Italian setting, the most cost effective diagnostic approach for general population screening is "Reflex testing" which means that HCV-RNA test should be performed on the same serological specimen with a positive anti-HCV finding in individuals who have never been previously tested for HCV infection [Marcellusi et al EASL Annual meeting 2021 Poster presentation S652 (PO-1374)]. Different solutions may work better in specific clinical settings, but as also suggested by EASL and WHO indications [12, 13] the use of reflex RNA testing for Ab-positive samples, could be considered as preferential diagnostic approach for HCV screening of individuals who are unaware of an HCV infection in each region. It can support increases in diagnosis, the streamlining of diagnosis cascade and subsequent treatment of infected patients. It has been shown that HCV RNA reflex testing is the most cost effective diagnostic approach being also affordable within the dedicated budget for HCV screening in Italy [3, 7].
- In the Services for Dependencies the Screening Ministerial decree indicate the Point-of-Care and Rapid HCV RNA Diagnostic Tests for people who actively use drugs in order to ensure the direct diagnosis and potentially linkage to care of individuals at high risk of infection [3, 7]. This indication should be carefully taken into the consideration in each Italian region in order to avoid the ongoing HCV transmission in drug users who represent the population with the highest infection burden and also at high risk of lost during diagnosis and care cascade, if the diagnosis is delayed.
- Simultaneously with the approval of the Milleproroghe Law decree for HCV free of charge screening in key populations and specific birth cohorts, the dedicated fund for the innovative non-oncological drugs was expired. Although the new HCV screening policies addresses key points for HCV elimination and a specific fund for HCV screening has been released for each Italian region, the lack of a dedicated fund for the DAAs would stress the regional budget. 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. The investment in treating newly diagnosed patients was translated into a significant reduction of liver disease complications with great economic benefits [14]. The evidences produced by National Center for Global Health of Istituto Superiore di Sanità and Center for Economic Evaluations of Tor Vergata University of Rome demonstrated a high cost benefits of treating patients diagnosed by screening. For 10,000 standardized treated patients diagnosed through an active HCV screening, over a 20-year time horizon there are

7,769 avoided events of progression which are associated with € 838.73 million net savings accrued by the Italian NHS. The initial investment in treatment is recouped in the form of savings from disease complications avoided in 4.3 year [15]. 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 [3, 14]. These evidences are helpful for the ongoing central and regional decision-making process. 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 [3].

- Patients' tailored therapy approach still remain a challenge. The Italian Medicines Agency (AIFA) have recently defined therapeutic equivalence between the pan genotypic DAAs. High efficacy of DAA treatment has been guaranteed up to date by a tailored and simplified therapy evaluated case by case considering specific clinical and socio-behavioural characteristics of treated population. The European Clinical practice guidelines for HCV infection emphasize the need to assess drug-drug interactions prior to starting the DAA therapy. "Prior to starting treatment with a DAA, a full and detailed drug history should be taken including all prescribed medications, over-the-counter drugs, herbal and vitamin preparations and any illicit drug use discussed and documented. The pre-treatment appointment can be used to rationalise prescribing. The pharmacokinetic profiles and how HCV drugs impact key drug-drug interactions and potential listing of drug-drug interactions, are reported in www.hep-druginteractions.org for a list of 800 co-medications" [12]. Based on the evidences of PITER cohort [16], which is one of the most representative Italian real life cohort which includes more than 10.000 patients with chronic HCV infection, enrolled about 60 Italian centers from all geographical macro areas, of patients with F0-F3 fibrosis stage, treated with different DAA regimens, 53-67% reported more than one comorbidity and 40-60 % of them reported more than one co-medication (33-37% of them more than 3 co-medications). As also reported by the PITER cohort over 70% of patients with F4/cirrhosis have reported comorbidities and co medications' use. In 10% of DAA treated patients, changes in the comedications have been required prior or during antiviral therapy. In addition, around 46% of patients treated with specific DAA regimens, careful/monitoring may be required or coadministration is not recommended (category 2 or 3 recommendations on potential DDI in their use with DAA regimens) [17]. Undiagnosed HCV infected individuals in Italy have different age group, disease severity, lifestyle and life's conditions. Drug users, yet to be diagnosed are estimated to be around 150,000 and in many of them different viral coinfections are also present [6]. Of patients from general population, around 100,000 are estimated to have a severe liver damage (F4/cirrhosis) for whom, an immediate linkage to care and a personalized DAA regimen with no or minimal drug-drug interactions is required [6].
- The COVID-19 pandemic will change the delivery of care forever and adjust our approaches to this pandemic, and to other future health demand accordingly. The possibility to eliminate an infection requires health systems to place greater focus on shifting from reactive to proactive care. This has been extensively focused worldwide in fighting SARS-CoV-2 infection. In the field of hepatitis, this includes the capacity to provide greater operational support where this is needed. With specific regard to the achievement of WHO hepatitis elimination goals, all measures that will be put in place during and after COVID-19 pandemic could be transferred in increasing diagnosis and linkage to care of people with hepatitis [14, 18, 19]. COVID 19 vaccination could be used to implement HCV screening, as it has been shown by successful initiatives conducted in different Italian regions.

Conflict of interest statement

No conflict of interest is declared by all the Authors regarding this paper.

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