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REVIEW

- 1664 Artificial intelligence in gastroenterology and hepatology: Status and challenges
Cao JS, Lu ZY, Chen MY, Zhang B, Juengpanich S, Hu JH, Li SJ, Topatana W, Zhou XY, Feng X, Shen JL, Liu Y, Cai XJ
- 1691 From hepatitis A to E: A critical review of viral hepatitis
Castaneda D, Gonzalez AJ, Alomari M, Tandon K, Zervos XB

MINIREVIEWS

- 1716 Paediatric gastrointestinal disorders in SARS-CoV-2 infection: Epidemiological and clinical implications
Al-Beltagi M, Saeed NK, Bediwy AS, El-Sawaf Y
- 1728 Hepatitis C virus micro-elimination: Where do we stand?
Mangia A, Cotugno R, Cocomazzi G, Squillante MM, Piazzolla V
- 1738 Coronavirus disease 2019 severity in obesity: Metabolic dysfunction-associated fatty liver disease in the spotlight
Vasques-Monteiro IML, Souza-Mello V
- 1751 Preoperative physiological esophageal assessment for anti-reflux surgery: A guide for surgeons on high-resolution manometry and pH testing
Yodice M, Mignucci A, Shah V, Ashley C, Tadros M

ORIGINAL ARTICLE**Basic Study**

- 1770 Protective effect and mechanisms of action of Mongolian medicine Sulongga-4 on pyloric ligation-induced gastroduodenal ulcer in rats
Tong S, Wang H, A LS, Bai TN, Gong JH, Jin WJ, Dai LL, Ba GN, Cho SB, Fu MH
- 1785 Depletion of MRPL35 inhibits gastric carcinoma cell proliferation by regulating downstream signaling proteins
Yuan L, Li JX, Yang Y, Chen Y, Ma TT, Liang S, Bu Y, Yu L, Nan Y
- 1805 Mitochondrial pathway of the lysine demethylase 5C inhibitor CPI-455 in the Eca-109 esophageal squamous cell carcinoma cell line
Xue XJ, Li FR, Yu J

Observational Study

- 1816 Health-related quality of life after curative resection for gastric adenocarcinoma
Grosek J, Zavrtnik H, Tomažič A

SYSTEMATIC REVIEWS

- 1828** Surrogate markers of mucosal healing in inflammatory bowel disease: A systematic review
State M, Negreanu L, Voiosu T, Voiosu A, Balanescu P, Mateescu RB

CASE REPORT

- 1841** Managing esophagocutaneous fistula after secondary gastric pull-up: A case report
Lock JF, Reimer S, Pietryga S, Jakubietz R, Flemming S, Meining A, Germer CT, Seyfried F

ABOUT COVER

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Hepatitis C virus micro-elimination: Where do we stand?

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Abstract

Hepatitis C virus (HCV) elimination by 2030, using direct-acting antiviral treatments, has been promoted by the World Health Organization. This achievement is not attainable, however, particularly after the 2020 pandemic of the coronavirus disease 2019. Consequently, the more realistic objective of eliminating HCV from population segments for which targeted strategies of prevention and treatment are easily attained has been promoted in Europe, as a valid alternative. The underlying idea is that micro-elimination will ultimately lead to macro-elimination. The micro-elimination strategy may target different specific populations and at-risk groups. Different settings, including prisons and hospitals, have also been identified as micro-elimination scenarios. In addition, dedicated micro-elimination strategies have been designed that are tailored at the geographical level according to HCV epidemiology and individual country's income. The main elements of a valid and successful micro-elimination project are reliable epidemiological data and active involvement of all the stakeholders. Community involvement represents another essential component for a successful program.

Key Words: Hepatitis C virus antibodies; Hepatitis C virus elimination; Hepatitis C virus epidemiology; Hepatitis C virus RNA; Hepatitis C virus diagnosis; Hepatitis C virus infection

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Core Tip: Achievement of hepatitis C virus (HCV) elimination using direct-acting antiviral drugs treatment by 2030 promoted by World Health Organization is hardly attainable especially amidst the coronavirus disease 2019 pandemic. The smaller goal of eliminating HCV from population segments for which tailored strategies of prevention and treatment can be easily implemented appears more realistic. Different

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specific populations and at-risk groups, as well as different settings including prisons and hospitals have been selected for micro-elimination campaigns. Dedicated micro-elimination strategies have also been designed at geographical level according to the countries income and HCV epidemiology. The success of micro-elimination depends on reliable epidemiological data and active involvement of all the different stakeholders.

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INTRODUCTION

Chronic hepatitis C is a major public health problem, affecting approximately 71 million people worldwide^[1]. In 2016, the World Health Organization (WHO) published a document highlighting their global strategy aiming to achieve viral hepatitis elimination by 2030^[2,3]. The objectives of this strategy for hepatitis C virus (HCV) infection-as a public health problem-are 90% reduction of new infections, 65% reduction in mortality, 90% increase in HCV diagnosis, and 80% increase in treatment rates.

The availability of low cost and highly efficient pangenotypic regimens for HCV treatment has led to the treatment of 5 million infected persons across the world. However, all the steps along the HCV care cascade need to be enhanced, starting with the proportion of infected people screened, followed by the number of patients testing positive for HCV antibodies and diagnosed with HCV RNA, and finishing with the consequent proportion of patients linked to care and treatment^[4]. While safety improvements and harm reductions can be achieved and will ensure a reduction in incidence, HCV diagnoses remain largely suboptimal, with less than 20% of the estimated 71 million chronic HCV-infected individuals identified globally. Razavi *et al*^[5] reported that, among high-income countries, only 11 are on track to eliminate HCV by 2030 and 5 more countries are on track for elimination by 2040; all the remaining are expected to eliminate HCV by 2050 or later. This is mostly due to an insufficient number of patients diagnosed, linked to care and treated, across the majority of countries.

A low level of community awareness as well as stigma and fears related to special populations, such as people who use intravenous drugs (PWID), prevent an expanded screening. Referral of patients already diagnosed represents another major challenge. Even more critical are geographical and transportation barriers. Long wait times before the start of treatment and reimbursement policies in some countries account for additional obstacles. Although pre-treatment evaluations, including viral load confirmation and liver disease staging, can be simplified using the pangenotypic and panfibrotic regimens currently available^[4], treatment restrictions related to the stage of fibrosis remain a limiting factor in several countries.

More recently it has become evident that a key aspect in improving the results of treatment strategies is patient engagement. In addition, the coronavirus disease 2019 (COVID-19) pandemic is having a deep impact on management of chronic liver diseases in general. Screening campaigns appear more difficult to implement, and testing and access to treatment have been reduced^[6]. Moreover, modeling the global impact of COVID-19 on global HCV elimination efforts has shown that a 1-year delay scenario could result in an excess of incidence of HCV cases and liver-related events among such cases, as well as an excess of cases with the infection's consequent hepatocellular carcinoma development^[7].

Thus, it is clear that a one-size-fits-all strategy would be unsuccessful to achieve global elimination and that different populations with chronic HCV infection require dedicated programs^[8,9]. Achievement of elimination in a well-defined group or context currently appears more feasible and checkable than a macro-elimination plan^[10]. The inclusion of key interventions and the adoption of test-and-treat strategies and simplified treatment regimens were then considered more tangible and achievable milestones. In particular, since 2017, the European Association for Study of the Liver

adopted a micro-elimination strategy as a stepwise, savvy approach in the fight against HCV. The goal of macro-elimination was accordingly adjusted in order to pursue micro-elimination in defined subgroups of patients, such as patients with human immunodeficiency virus (HIV)/HCV coinfection or hemophilia, and prisoners or PWID^[10].

Micro-elimination requires involvement of all the different stakeholders, including administrative local representatives, health providers, and patients representatives. This strategy is based on different criteria that allow stakeholders to adapt to different situations. The key aspect is to individualize access to the services on the basis of the patients' needs in order to overcome barriers and to achieve higher rates of diagnosis and treatment in a given population of interest during an established period of time. It is important that the progress attained is publicly announced and analyzed using adequate performance indicators^[11]. One of the advantages of this strategy is that once results are achieved in a given context, the success translates into leverage for new initiatives. Of course, stakeholders' engagement is key to successful micro-elimination, together with funding, advocacy efforts and ability to scale, and most importantly involvement of the community. The approaches to micro-elimination may differ and they might be based on different locations, different settings, or different populations^[11].

AVAILABLE HCV TREATMENT REGIMENS

Current developments in the treatment of chronic hepatitis C are dramatic. Indeed, several direct-acting antiviral drugs (DAA) have been approved from 2013 to 2017 for treatment of HCV-infected patients, with high rates of sustained virological response (Table 1). The arrival of these highly effective treatment regimens has improved prospects for the eradication of HCV worldwide. DAA are well tolerated. The first approved DAA was sofosbuvir a once-daily pangenotypic oral nucleotide analog polymerase inhibitor as a component of combination antiviral regimens. It was approved on December 2013^[4]. The protease inhibitor simeprevir was used as a two pills combination with sofosbuvir for all the different HCV genotypes but 2 and 3 on 2014^[4]. Sofosbuvir was later in the same year used as a single pill fixed dose combination with the NS5A inhibitor, ledipasvir for genotype 1 and 4 treatment^[4]. Simultaneously, on 2014 the three compounds combination of ombitasvir, paritaprevir /ritonavir boosted and dasabuvir not including polymerase inhibitor was approved for genotype 1 treatment^[4]. Daclatasvir another NS5A inhibitor was approved for genotype 2 and 3 on 2015^[4]. The combination of NS5 and NS3 protease inhibitor elbasvir and grazoprevir with or without ribavirin for GT1 and 4 infection was approved on 2016^[4]. However, the true revolution was the approval on January 2016 of sofosbuvir/velpatasvir (SOF/VEL). Velpatasvir is a second generation NS5A inhibitor administered with sofosbuvir as single pill fixed combination^[4]. This was the first pangenotypic regimen to be used without ribavirin for 12 wk regardless of severity of liver disease even in patients with compensated cirrhosis^[4]. The other pangenotypic regimen based on glecaprevir and pibrentasvir without the inclusion of a polymerase inhibitor to be administered as three pills daily initially for a variable duration of treatment of 8 or 12 wk and later for only 8 wk in patients with or without cirrhosis infected with genotypes 1, 2, 4 and for no cirrhotic genotype 3 and for 12 wk in patients with cirrhosis of genotype 3 was approved on 2017. The use of easy to manage and safe pangenotypic regimens provide not only effective treatment options but also the most powerful opportunity to achieve HCV elimination.

MICRO-ELIMINATION IN DIFFERENT GEOGRAPHICAL LOCATIONS

Egypt has a very high burden of HCV infections and severe HCV-related liver diseases. In 2015, the reported prevalence of HCV chronic infection in the general population was 7%^[12]. The national plan involved testing of 35 million Egyptians for HCV antibodies, over a 6-mo period. As a result, over 2.4 million Egyptians had been treated by 2019. This is an example of strong political commitment and industry support, allowing barriers to be removed. However, implementation of systems to track patients who were treated and cured, and to monitor the achievement of HCV elimination have not been properly developed. Pilot projects conducted at community level were recently completed^[12]. From 2018, a test-and-treat strategy was started, targeting each individual aged 18-80 years in 73 villages under the auspices of 7

Table 1 Treatment compounds available for hepatitis C virus infection

	No cirrhosis		Cirrhosis (Child-Pugh class A)	
	Naïve	Experienced	Naïve	Experienced
HCV-1a, 1b, 2, 4, 5	SOF/VEL 12 wk	SOF/VEL 12 wk	SOF/VEL 12 wk	SOF/VEL 12 wk
	GLE/PIB 8 wk	GLE/PIB 8 wk	GLE/PIB 8 wk	GLE/PIB 12 wk
	GZR/ELB (GT 1b or 4 only) 12 wk	GZR/ELB (GT 1b or 4 only) 12 wk	GZR/ELB (GT 1b or 4 only) 12 wk	GZR/ELB (GT 1b or 4 only) 12 wk
	SOF/VEL/VOX 8 wk	SOF/VEL/VOX 8 wk	SOF/VEL/VOX 12 wk	SOF/VEL/VOX 12 wk
HCV-3	SOF/VEL 12 wk	SOF/VEL 12 wk	SOF/VEL 12 wk	SOF/VEL 12 wk
	GLE/PIB 8 wk	GLE/PIB 12 wk	GLE/PIB 8-12 wk	GLE/PIB 16 wk
	SOF/VEL/VOX 8 wk	SOF/VEL/VOX 8 wk	SOF/VEL/VOX 8 wk	SOF/VEL/VOX 8 wk

SOF: Sofosbuvir; VEL: Velpatasvir; GLE: Glecaprevir; PIB: Pribentasvir; EBR: Elbasvir; GZR: Grazoprevir; VOX: Voxilaprevir; HCV: Hepatitis C virus.

governates. Free testing was offered, and patients were linked to care and offered free treatment during an educational and prevention campaign. Of the 200000 early tested individuals, 34000 tested positive for HCV antibodies and 14500 were treated. Of those, 99.9% completed the assigned treatment and 97% achieved viral clearance^[13].

Another example of a well-conducted HCV micro-elimination campaign comes from Iceland, where the HCV prevalence before the direct-acting antivirals revolution was low. Of 1000 persons infected with HCV in the country, nearly all have been diagnosed within a test-and-treat campaign started in 2016. Treatment was supported by pharmaceutical companies. So far, the island is on track to eliminate HCV by 2021^[14].

Georgia was the first European country that started an active national hepatitis elimination program tailored to local needs, based on the 5.4% HCV prevalence in the country. A nationwide case-finding integrated program was designed according to previous experiences in HIV prevention and a control program was initiated for HCV^[15]. The HCV testing was integrated in the country's healthcare services for substance users, patients with mental health disorders, and HIV-coinfected subjects. The initial program expanded its scope in 2016, aiming for complete HCV elimination. Of the 150000 estimated HCV-infected subjects, 58% were diagnosed and 80% initiated the HCV treatment; the cure rate was 98.8% for those who completed it. Identification of HCV infection among the remaining population appears to be challenging. According to a recent model based on the Georgia data, in 2019, mortality was reduced by 14% and both prevalence and incidence were reduced by 37%^[16].

Among the other European countries, Scotland raised awareness on the impact of HCV through strong campaigns. This led to political support in scaling up the issue, with consequent reduction in HCV incidence and prevalence as well as in mortality. The improvements in harm reduction settings were mainly driven by the use of rapid and accurate diagnosis through dried blood spot testing. Given that there remain undiagnosed subgroups, the next challenge will be involving primary care physicians to increase the diagnosis rate and treatment access^[17]. In Spain, with 46.9 million inhabitants and an HCV prevalence of 0.22%, a nationwide plan was initiated in 2016. According to the national data, while HCV testing has been performed in 90% of the general population, testing and linkage to care in at-risk groups remain suboptimal^[18].

In other countries, including some from Europe and the United States, the lack of comprehensive data on local situations in terms of prevalence and incidence, or the lack of good quality data in given high-risk groups-other than the lack of affordable tests or harm reductions programs-seem to be affecting achievement of the WHO's goal.

In particular, HCV elimination in low- and middle-income countries has been considered prohibitive until recently. Low-cost screening and drop of drug cost attained only recently are the cornerstone of a published experience involving Cambodia, India, Indonesia, Myanmar, Nigeria, Rwanda and Vietnam by intensive screening and decentralized programs this program has led to cure over 120 people with cure rate higher than 90%. This initiative-supported by Clinton Health Access-proves that the combination of political will, modest financial investment and adequate training pave the way for viral elimination even in the presence of limited

infrastructures^[19].

Exploring worldwide progresses in the path to achieve a testing cure protocol for HCV, special attention needed to be reserved to Pakistan. Pakistan has the second highest global burden of HCV infection worldwide with very low level of infection awareness^[20]. The Government launched a National Hepatitis Framework for 2017-2021 planning to cure 95% of infected people with DAA (generic sofosbuvir in combination with ribavirin). This initiative resulted in a doubled number of treatments. Despite this success, the country should develop an extensive monitoring and evaluation system and should further implement the national plan^[21].

Moving to other countries, low testing rate and poor linkage to care are barriers to treatment in China. Due to its large population a considerable number of infected patients have not yet been discovered. In order to curb the spread of HCV infection and relate morbidity hospitals conduct blood-borne virus screening for inpatients^[22]. In addition, several projects are exploring the impact of social media in increasing HCV infection awareness. Among them an interesting randomized controlled study based on crowdsourcing is ongoing in Shenzhen in the setting of primary care. This study aims at enrolling more than 1000 subjects older than 30 years. Subjects randomized into the active arm will receive promotional material by social media campaigns and their HCV testing uptake will be compared to those of the control group just attending the primary care departments and not involved in crowdsourcing activities^[23]. A model of targeted HCV screening in past PWID has been adopted in Hong Kong since 2012. Although based on a limited number of subjects, this project represents the first example of targeted screening in Asia^[24].

MICRO-ELIMINATION IN DIFFERENT SETTINGS

Prisons' and hospitals' emergency departments are considered appropriate settings for universal screening programs. HCV is common in prisons and guidelines recommend that HCV treatment should be offered to all HCV-infected prisoners. However, a significant proportion of incarcerated patients remain untreated and, once released, contribute to the spread of HCV through the local community. The incidence of HCV infection among prisoners is consequent to drug use and has been estimated globally as 16 *per* 100 person-years (1-34 years)^[25]. Prisoners are difficult to engage, due to established high-risk behaviors and psychological disorders^[26]. On the other hand, the specific context of prisons allows, after a rapid testing, a quick treatment plan implementation and completion, with the only limiting factor being a short permanence in the same prison^[27]. A study conducted in Australia showed that of 562 HCV RNA-positive patients, 416 started treatment with different direct-acting antiviral agents. A sustained virological response (SVR) at 12 wk of 72% was attained, with patients lost to treatment after release accounting for this particular SVR rate. For patients able to complete treatment, per protocol analysis revealed higher SVR at 12 wk (SVR12) rates, up to 96% and comparable to those for the general population^[28]. This study was based on a nurse-centered strategy.

Other models based on multidisciplinary networks and telemedicine have been explored in the United Kingdom^[29]. Initiatives based on telemedicine were promoted and associated with a high number of treatments and treatment responders in Spain, in a large experiment conducted in "El Dueso" prison between May 2016 and July 2017. Overall, 847 inmates agreed to participate. Among them, 110 were HCV antibodies-positive and 86 HCV RNA-positive. Only 69 patients were treated and 66 of those completed the treatment, yielding a 96.9% SVR rate by intention-to-treat analysis^[30]. In the United Kingdom, 128 of 266 individuals who started treatment based on telemedicine had available follow-up data. Of them, 87% achieved SVR; however, the proportion of patients who experienced reinfection was high^[31].

The feasibility of a test-and-treat strategy in incarcerated subjects has been highlighted recently in a study by Wong *et al*^[32]. This study was based on a pangenotypic regimen, with minimal monitoring required. Of the 526 incarcerated adults treated with SOF/VEL in different countries across the world, SVR12 was attained by 437, representing 98.9% of those who completed treatment. A non-virological failure was reported in 82 individuals.

Another example of micro-elimination in a dedicated setting is provided by various interventions implemented in hospital emergency or surgical departments. Examples of these strategies are provided by studies conducted in Spain, in Italy and, more recently, in the United States. In a Spanish study conducted at the emergency department of Hospital Val d'Hebron on 5000 subjects, it was shown that the rate of

HCV antibodies positivity was 4%, higher than that in the general population; in contrast, the rate of active infections was low, with only 16% being HCV RNA-positive. Interestingly, the study showed that in 40% of cases, patients were unaware of their infectious condition^[33].

An Italian survey evaluated 11000 patients from the Venetian area. Each patient was tested upon admission to the surgery department^[34]. Overall, 2% showed HCV antibodies positivity. Again, the rate was slightly higher than in the general population. Unfortunately, in this study, the results from HCV RNA data were not available for all and estimating active infections was not possible.

In the United States, an automated emergency department cohort screening for viral hepatitis was started in 2018 in New Jersey. The strategy was based on testing Baby Boomers until 2019 and was implemented by extending screening to at-risk in-patients from 2019 to 2020, with further expansion of the screening according to the Centers for Disease Control (CDC) screening guidelines from 2020 onwards. With the aid of a patient navigator, subjects testing HCV RNA-positive were linked to treatment. Universal screening results showed a 3.4% rate for HCV antibodies positivity and 0.9% of HCV RNA positivity among missed Baby Boomers subjects; the rates among non-Baby Boomers were 0.8% and 0.2%, respectively. Rates were higher for subjects aged 55-75 years. The combined cohort and universal screening led to identification of 195 infected individuals among the 37000 subjects who were screened to be linked to care^[35].

MICRO-ELIMINATION IN DIFFERENT POPULATIONS

As reported by Degenhardt *et al*^[36], the estimated prevalence of PWID by country is variable, with the highest rates reported in United States, Russia, Australia, Brazil, and the European Union. In the United States, PWID account for 60% of new HCV infections (60%) (CDC 2018), while in the European Union, 53.2% of PWID are reportedly HCV antibodies-positive. In the United Kingdom, 80% of individuals infected with HCV are PWID. Therefore, PWID are a key population for targeted micro-elimination strategies. In this population, pangenotypic regimens are associated with high rates of SVR, regardless of the recent use of substances^[37].

A large number of studies have investigated different strategies to eliminate HCV in this target population. Integrated approaches based on harm reduction in community settings to enable scale-up and use of simplified models based on low-cost diagnostics have been shown successful in improving screening, linkage to care, treatment access, and response. Studies have suggested that scale-up treatment in this population is mandatory^[38]. A study conducted in Scotland in Tayside, a region with a population of 400000 and with an HCV prevalence of 0.55%-0.56%, explored enhanced testing and treatment service focusing on the HCV/HIV coinfection subpopulation. Of the total 2700 subjects, 2300 were diagnosed. In comparison to the pegylated-interferon treatment era, higher rates of patients were linked to treatment and cured. Multidisciplinary involvement included pharmacies, drug treatment centers and prisons, and was based on dedicated educational programs. Of the positive patients, 76% were treated^[39].

Multidisciplinary involvement has been pursued by other groups, including ours. In late 2019, our center launched a program promoting ad hoc transportation from "SERDS" (*i.e.*, Centers Taking Care of People with Substance Disorders) to prescribing centers, fast-track baseline evaluation at our center, and a close on-treatment monitoring at 15 different SERDS by the SERDS physician. Of 1500 patients screened, 239 (16%) were HCV RNA-positive, and all were linked to care and started treatment. Of them, 30% were active drug users and 70% were past drug users. High SVR12 rates were reported overall, being 98%. No reinfection was experienced during a short follow-up^[40].

Other initiatives, within substance users disorders programs, have targeted their efforts to decentralization. Among them, one-within a continuum program adopted in Philadelphia, United States to compare navigator *vs* embedded treatment models-recently showed that navigators are not sufficient to link HCV PWID to HCV cure^[41]. By contrast, embedding HCV treatment within a substance use disorders (SUD) treatment program increases the number of patients linked to care.

The feasibility of HCV eradication in intravenous drug use in Italy has been evaluated within the San Patrignano Therapeutic community. Results showed that one-third of the resident patients were unaware of their HCV infection status. The rate of HCV antibodies-positive patients was 65%, and 238 of the 293 patients who tested

HCV RNA-positive started treatment. As in our study, no case of reinfection was experienced after a short follow-up^[42]. The SVR rate was 96.6%. In both these studies, patients were treated with a pangenotypic regimen of SOF/VEL for 12 wk.

Decentralization of the confirmatory testing in harm-reduction sites has been recently implemented. Test-and-treat in point-of care at harm-reduction and addiction centers was proposed as a strategy to treat patients monitored at these centers or at addiction centers in Catalonia, Italy^[43]. In both cases, an increase in the number of treatments was registered (+ 57% and + 19%, respectively), although SVR remained suboptimal and associated with a reinfection rate of 6% in harm-reduction centers^[43]. In Georgia, a decentralizing screening strategy was shown to be associated with an increase in every step of the HCV care cascade^[44]. In the United States, decentralization was implemented with an internist addiction medicine specialist evaluating opiate-dependent patients in a hepatology clinic. This co-localization model was associated with an improvement in the number of patients taking treatment, with an adherence rate of 87.4% and SVR of 98.9%^[45].

Among the higher risk groups, MSM cannot be forgotten. Data from population based on systems evaluating the progress through the cascade of care in this group are limited. In France, incidence continue to rise. Among 21,519 HIV positive, HCV negative patients followed between 2012 and 2016 in 16 centers, 218 first HCV infections occurred. Simultaneously, among 3392 patients with cured HCV infection, 74 reinfections were registered^[46]. This data show why this is a target population for micro-elimination even despite the high uptake of DAA. As shown in a study from Switzerland, DAA use was able to halve HCV incidence in HIV positive MSM^[47].

Very recently a study was designed to compare progress in care and treatment in MSM and non-MSM with HCV infection living in British Columbia^[48]. Slightly more MSM *vs* non-MSM received HCV RNA confirmatory testing (83% *vs* 82%) and initiated treatment. In 2019 as compared to 2012, treatment uptake among MSM increased significantly (63% *vs* 37%). SVR rates of 91% and 90% were registered among MSM and non-MSM, respectively. These results suggest that DAAs were associated with substantial improvement in progression across the different HCV care cascade steps.

COVID-19 CHALLENGES CAN HELP HCV SCALE-UP

COVID-19 emergency is demonstrating a greater impact in HCV testing and diagnosis. In United States, at Boston Medical Center, testing decreased by 50, while new diagnoses decreased by more than 60%^[49]. Consequently, nontraditional methods of preventive healthcare delivery as telemedicine and technology need to be used in order to emphasize the importance of prevention.

In African Countries integration of diagnostics platforms and implementation of digital technologies were rapidly promoted during the pandemic. Testing and treatment services are facilitating the continuation of essential prevention and are ensuring that people are not further marginalized. Although prevention interventions that require mass gathering are suspended, internet and postal systems may ensuring treatment distribution and help is assisting patients with self-testing^[50].

CONCLUSION

The simplification of treatment access, and treatments tailored to the different settings are key aspects towards achieving HCV elimination. All the described interventions have demonstrated an ability to increase in one or more of the HCV cascade steps. The success of micro-elimination initiatives relies on correct targeting of a patient population or appropriate geographical context identification and patient setting.

The COVID-19 pandemic is affecting the results of some of these initiatives, requiring an extension of the timelines and further adjustments to reduce interpersonal contacts. However, it may also result in opportunities to spread awareness of the risks related to infectious disease and of the chances of combined screening programs for HCV and COVID-19.

As the WHO goal for HCV elimination seems hard to reach in the proposed timeframe, micro-elimination is a key alternative strategy. Provided that community involvement represents a free pass for a successful program, micro-elimination will ultimately lead to macro-elimination.

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