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Review

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Direct-acting antivirals and chronic hepatitis C: towards elimination

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Abstract

Hepatitis C virus (HCV) is a major cause of liver morbidity and mortality worldwide with increasing disease burden projected for the next several decades. The timely advent of direct-acting antivirals (DAAs) sparked significant public health responses aimed at HCV elimination by 2030. This review will focus on the implications of the DAAs in terms of medical progress, barriers to HCV elimination as a public health threat, and current gaps that will require further innovation. We utilized PubMed searches with the relevant keywords for articles published in the last 5 years, as well as personal collections of relevant publications. DAAs have proven to be safe and effective. DAAs are well suited for nearly all infected patients, and many countries worldwide have taken on initial treatment scale-up strategies. These unprecedented efforts, albeit significant, face extraordinary challenges related to the high infection burden, stigma, and financial constraints. Currently, few countries are progressing towards HCV elimination, as this attainable public health goal requires explicit, adequately resourced, and coordinated public health prioritization at all levels.

Keywords: Direct-acting antivirals, hepatitis surveillance, hepatitis C elimination

INTRODUCTION

Chronic hepatitis C virus (HCV) is a blood-born viral infection that affects over 71 million people worldwide, representing a major cause of liver morbidity and mortality[1-3]. HCV chronically infects hosts as a complex mixture of related variants or "quasispecies", able to genetically evolve and escape host immune responses[4]. Paradoxically, HCV-specific cytotoxic T-cell immune responses lead to hepatocyte injury, liver fibrosis progression and complications [cirrhosis and hepatocellular carcinoma (HCC)][5]. Although no effec-

tive vaccine is currently available, HCV infection is amenable to cure if potent antivirals fully and quickly suppress virus replication. Sustained virologic response (SVR), i.e., cure, is achieved following therapy completion in > 95% of treated individuals[6,7]. Direct-acting antivirals (DAAs) have shown superior safety and efficacy compared to interferon-based regimens (> 95% *vs.* 40% cure rates, respectively), and revolutionized HCV treatment paradigms towards broader access to cure[8]. The 69th World Health Assembly endorsed the global health sector strategy to eliminate HCV infection by 2030, which can become a reality with expanded use of DAAs[9]. Here, we describe the current prospects of HCV eradication in the DAA era and ongoing challenges to achieve elimination goals.

CLINICAL IMPACT OF DIRECT-ACTING ANTIVIRALS

In 2012, Lok *et al.*[10] reported successful treatment of patients who were null responders to peg-interferon and ribavirin, infected with genotype 1a and 1b HCV, who received a 24-week course of asunaprevir, a protease inhibitor, and daclatasvir, a non-structural protein 5A inhibitor. This preliminary, proof of concept study demonstrated that SVR (virologic cure) could be achieved by the combination of two DAAs in patients who did not respond to the standard of care at the time. It also signified the culmination of a sequence of major breakthrough discoveries that followed the cloning of HCV for the first time in 1989[11]. Such progress in basic science allowed, over the ensuing years, for elucidation of key functions of the HCV genome and the virus life cycle; engineering of "sub-genomic" replicons; and development of functional cell-based *in vitro* systems suitable to screen compound candidates for effective treatment[12,13]. Lok's study led the way of an impressive wave of clinical studies, that applied several combinations of DAAs at an extraordinarily fast pace[14]. From these clinical studies, we learned that DAAs proved to be safe and effective in addressing unmet needs of key subpopulations, traditionally unreached by interferon-based therapies. State-of-art treatment options were made available for patients with human immunodeficiency virus (HIV) co-infection[15-22], decompensated cirrhosis[23-28], post-liver transplantation[29-33], chronic kidney disease[34,35], renal transplant patients[36-38], and children[39,40]. These clinical studies also defined best practices in overcoming HCV resistance. Highly efficacious retreatment strategies could still be utilized for the few patients experiencing DAA-failure and emergence of resistance associated substitutions[41-46].

The field quickly evolved towards the recognition that HCV can be eradicated from most, if not all, infected individuals, expanding the benefits of virus clearance[47]. Virologic cure has been shown to universally decrease liver inflammation, reflected by improved aminotransferase levels and reduced rates of liver fibrosis progression. In some patients, achieving SVR also leads to cirrhosis regression and improvement in clinical signs of portal hypertension and end-stage liver disease[48]. Numerous studies have demonstrated strong associations between SVR and significant reductions in the risk of HCC, liver-related mortality and liver transplantation[49-51]. In addition to these major clinical benefits, cure of HCV infection ameliorates or facilitates management of extra-hepatic manifestations such as cryoglobulinemia, non-Hodgkin's lymphoma, diabetes and porphyria cutanea tarda[52-54]. The lower complexity of DAA therapy has made investigators and clinicians challenge the preconceived notion that expeditious HCV treatment would only benefit highly selected patients who exhibited liver fibrosis METAVIR stage 2 at a minimum[55]. Well-designed cohort and modeling studies have suggested that early therapy in patients with no significant liver fibrosis have tremendous clinical benefits with SVR[56-58]. Similarly, patient reported outcome assessments from pivotal DAA trials have shown improvements in overall health-related quality of life and work productivity following successful HCV therapy[59-61]. These findings build on previous studies reporting reductions in fatigue after HCV cure with interferon and ribavirin[62]. Taken together, this body of work highlights the extraordinary clinical benefit potential of expanding use of DAAs [Table 1].

In addition, the medical field has clarified the lack of accurate data regarding HCC risk following DAA therapy[63,64]. Initially, concerns were raised that abrupt HCV viral load suppression using DAAs could hypothetically abolish the immune system surveillance or "brake" defenses to tumor progression. Further meta-

Table 1. Benefits of hepatitis C cure by scaling-up direct-acting antivirals

Primary prevention	Cirrhosis among patients with chronic infection
Clinical	Decreased liver inflammation Reduced rates of liver fibrosis progression Cirrhosis regression Potential improvement in portal hypertension and ESLD Improved management of extra-hepatic manifestations Reductions in insulin resistance Improved energy, cognition and quality of life measures
Secondary prevention	HCC among cirrhotic patients Liver-related mortality and liver transplantation AI disorders, PCT, B-cell non-Hodgkin's lymphoma All-cause mortality
Public health	Expanded cure to special patient populations with unmet needs Cure access to hard-to-reach populations (PWIDs, homeless) Scale-up programs with disease eradication goals
Societal	Cost-effectiveness potential Direct and indirect economic impact Awareness of patients, families, providers and health systems Reductions in stigma Integration and expansion of harm reduction programs

ESLD: end-stage liver disease; HCC: hepatocellular carcinoma; AI: auto-immune; PCT: porphyria cutanea tarda; PWIDs: people who inject drugs

analysis studies, however, demonstrated that (1) HCV cure following DAA therapy in patients with cirrhosis reduces HCC risk to a similar extent as interferon (IFN)-based cure (estimated at 63%-77% reduction); and (2) the beneficial impact on HCC incidence should be markedly higher in the DAA era, given the greater extent that cirrhosis populations are treated with DAAs, and the higher cure rates among these high risk patients[65]. Expanded use of DAAs will solidify the evidence in favor of decreased HCC risk following DAA-based virologic cure, as exemplified by the study findings of Backus *et al.*[66], which showed a 83.5% reduction in HCC diagnosis following DAA therapy.

Applying interferon-based HCV therapy among people who inject drugs (PWID) was extremely challenging due to patient, provider, health system, structural, and societal barriers[67-69]. The availability of DAA therapies with cure rates > 95% have overcome many of these barriers for PWID as they have fewer psychiatric side effects, are simpler (oral, once-daily *vs.* weekly injections), and shorter in duration. In earlier years, interferon-based therapy had been proved to be safe and effective among PWID[70], and results of several recent studies have provided substantial insight about DAA use among several PWID subgroups. Among people receiving opioid substitution therapy (OST) with no recent illicit drug use, post-hoc analyses of phase 2 and 3 trials of DAA therapy have demonstrated that the SVR is similar in those receiving and not receiving OST[71-75]. In the first phase 3 trial to evaluate DAA therapy in people receiving OST, including those with ongoing drug use, treatment completion was 96%, 97% demonstrated > 95% adherence, and the overall SVR was 91%[71]. Real-world results, among people with a history of injecting drug use (with and without recent drug use), indicated overall treatment completion rates of 93%-100% and SVR rates of 80%-96%[76-79]. In studies focused on people with recent injecting drug use, 95%-96% of participants completed therapy with SVR rates of 93%-94%[80,81]. Mathematical modelling adds further support to this strong body of evidence. According to these models, modest scale-up of DAA treatment to 8 per 100 PWID years could lead to substantial reductions in HCV prevalence within these populations, thereby preventing transmission and lowering HCV incidence[82,83]. Guidelines from the World Health Organization (WHO), the American Association for the Study of Liver Disease/Infectious Diseases Society of America, the European Association for the Study of the Liver, and the International Network for Hepatitis in Substance Users now recommend DAA treatment for PWID[84-87].

While associations between virologic cure and decreased the risk of liver disease-related death have been established during the interferon-era, all-cause mortality is still the most definite clinical end point with clear interpretation, and an important parameter in considering efforts for DAA treatment scale-up[50]. Van

der Meer *et al.*[50] were able to detect all-cause mortality benefit among patients with chronic HCV infection and advanced hepatic fibrosis who achieved SVR to interferon-based treatment. However, the retrospective nature of the study could have led to selection of a relatively healthy cirrhotic HCV population, because interferon therapy is contraindicated in patients with moderate to severe cirrhosis[50]. This selection bias is minimized by DAA therapies due to improved safety and efficacy profiles, even among patients with higher Model for End-Stage Liver Disease (MELD) scores. There is much anticipation to observe data regarding both all-cause and liver-related survival benefits, as the experience with DAA therapy accumulates. At the latest European Association for the Study of the Liver conference, Calvaruso *et al.*[88] reported results from a large real-world setting cohort with patients using a variety of DAA regimens. According to the authors, achieving SVR significantly reduced mortality from both liver disease-related and unrelated causes at all stages of liver fibrosis. In another report from the same conference, the European Liver Transplant Registry reported that, while the total number of liver transplants performed in Europe remained stable over the last decade, the percentage of transplants related to HCV fell significantly from 23% in the interferon era to 11% in the DAA era[89].

BARRIERS TO HCV ELIMINATION

The global burden of viral hepatitis is increasing since 1990, reaching 1.46 million deaths in 2013, exceeding that of HIV (1.3 million), tuberculosis (1.2 million) and malaria (0.5 million deaths). HCV is responsible for approximately 30% of the overall viral hepatitis mortality[90]. The advent of DAA therapy and its extraordinary clinical impact hold promise that HCV elimination as a public health threat is a reachable goal by 2030. According to the global health sector strategy on viral hepatitis 2016-2021, HCV elimination can be achieved by diagnosing 90% of people infected and treating 80% of the people diagnosed. Such a strategy is predicted to reduce new infections by 90% and mortality by 65%[9]. This report also established a baseline for tracking progress of this global strategy, where only 20% (14 million) of 71 million people living with chronic HCV knew their diagnosis and a disappointing 7.4% of those diagnosed (1.1 million) started HCV treatment in 2015.

DAAs can only benefit patients who are screened, diagnosed, linked to care, engaged in care and treated[91]. The HCV care cascade concept, adapted from public health efforts in HIV, identifies multiple missed opportunities to address the HCV burden at local, national and global levels[92,93]. In order for each HCV infected individual to move down the cascade from diagnosis to HCV treatment, a myriad of variables interact with each other in multifaceted ways. Adapted health care utilization frameworks, such as the Gelberg-Andersen model, are useful tools to examine and understand factors influencing the impact of specific care actions (such HCV screening, linkage to care, engagement, treatment initiation) among vulnerable, high-risk populations[94]. Health care utilization is in general influenced by traditional predisposing (ethnicity, age, education, gender), enabling factors (source of care, health insurance, income) as well as need (perceived health, medical conditions, awareness of HCV-positive status). For instance, progressive movement of HCV-positive homeless individuals down the cascade would also be influenced by additional, more specific predisposing (histories of child abuse, jail/prison, drug and alcohol use, mental illness, and risky sexual behavior), and enabling factors (barriers to care, competing needs, lack of housing, food security, and case management). It is known that the many of the highest HCV prevalent populations (i.e., PWID, homeless and socioeconomically disadvantaged) often lack access to HCV testing and continuity of care[94]. Case management and regular sources of care attenuates social vulnerability, and robust support systems are needed in response to these complex and challenging demands[95-97].

Several determinants of health care utilization among vulnerable individuals, including illicit drug use, often introduce stigma to the care cascade equation, furthering the hardships of those in need of HCV care and cure[98]. Perceived stigma associated with HCV infection leads to anxiety, fear of transmission to others, reduced intimacy in relationships, denial (reluctance to seek medical care for addiction and/or HCV

treatment) and social isolation[99]. People living with HCV are frequently blamed for the disease, putting themselves at risk to acquire HIV infection, and viewed as irresponsible, not accountable, "unworthy"[100,101]. Perceived and real stigma towards HCV, within families and workplaces, affect self-esteem and quality of life, causes delay or impediment to timely diagnosis and treatment, and leads to continuing risk of disease transmission[102]. The response to stigma requires broad-based, societal educational efforts in order to increase the understanding of this disease, still connected to several pejorative stereotypes[103,104]. These efforts are expected to bring greater compassion, patient-centered healthcare, and improved coping skills to people living with HCV[105].

Among the 71 million people infected globally, there is a large burden of HCV infection among PWID, with a 50% prevalence of chronic infection, representing an estimated 5.6 million individuals - 8% of all infections globally[106]. There is also a large and unquantified number of chronic infections among PWID who have ceased injecting, and HCV morbidity and mortality continues to rise among recent and former PWID[107]. In 2015, there were 1.7 million new HCV infections globally - this is a greater number than patients who were started on treatment in the same year - with 23% of these new infections attributable to current injecting drug use in many settings[9,108-111]. Along with unsafe healthcare practices and injections, intravenous drug use is a leading contributor to HCV incidence, especially in the European and Eastern Mediterranean Regions[9]. Even in areas of the world where the incidence was low in 2015, an increase in transmission may occur at any time, due to epidemic spread associated with injection drug use. Despite years of HCV decline in the US, the incidence of HCV infection doubled between 2010 and 2014, due to an intensifying opioid epidemic and rise in injecting drug use behavior[112]. The number of reported cases of acute HCV among persons reporting injection drug use has increased, particularly in rural areas[113,114]. In the US, injection drug use among PWID has resulted in rapid dissemination of HIV and HCV, as well as some transmission of hepatitis B virus (HBV)[115,116]. There have been few studies evaluating the HCV cascade of care among PWID, and contemporary studies from Australia and Kentucky has similarly shown high prevalence of antibody positivity, poor rates of viral load confirmation and minimal rates of treatment uptake, both during the interferon era and in the first few years of the DAA era[117,118]. In the Netherlands, access and reimbursement for DAA therapy occurred earlier (since 2014) than many other countries, and cohorts of PWID have been well-characterized. Despite rates of viral load testing as high as 95% among seropositive individuals, DAA uptake has remained low, largely limited by fibrosis staging restrictions that were in effect until October 2015 and subsequently lifted[119].

Transmission of HCV among men who have sex with men (MSM) infected with HIV has also been reported in Europe, Australia and the US as well as reinfection among HIV-infected MSM who were successfully cured with treatment for hepatitis[120,121]. No estimates are available to quantify how much this emerging issue contributes to the overall transmission of HCV[122,123]. The observed risk of reinfection in HIV-infected MSM during the interferon era ranged from 5.3 to 13.2/100 persons years[121,124,125], including subgroups with multiple HCV reinfections and at risk of transmission of HCV virus with resistant variants[121,126]. These reinfection rates are higher than the rates observed in retrospective and prospective studies of PWID treated for chronic HCV infection, ranging from 1.21 to 4.9/100 persons years[127-130]. The role of HIV infection in increasing the risk of HCV reinfection is likely associated with an approximately threefold reduction in rates of spontaneous clearance following acute HCV infection, as well as high-risk sexual practices among predominantly male cohorts representing HIV-infected MSM[131,132]. Traditionally, individuals at risk of reinfection have been grouped as either HIV-infected MSM or PWID; however, there is clearly a subset of HIV-infected men who both use injection drugs and have sex with men. As such, interventions targeted at both safer sexual practices and safer drug use practices are indicated among HIV-infected MSM.

HCV is highly prevalent among incarcerated populations, with global prevalence over 10%, and considerably higher among incarcerated PWID[133-135]. Globally, more than 10 million people are incarcerated on a daily basis, with many more annually, making prisons a key setting for implementation of HCV elimination strat-

egies[136]. The close relationship between injecting drug use, incarceration, and prevalence of blood-borne viruses makes correctional centers a crucial setting for enhanced DAA therapy access and broad prevention strategies[134]. The United Nations Basic Principles for the Treatment of Prisoners state that prisoners "shall have access to the health services available in the country without discrimination on the grounds of their legal situation"[137]. Unfortunately, this principle has been infrequently applied in real life and in most countries prisoners have a lesser possibility of assistance and care than other citizens[138]. Once in prison, overcrowding, violence, separation from family and emotional problems are additional reasons that may induce inmates to start or continue unsafe habits, fueling high incidence rates that exceeds 30 per 100 persons per year[139-141]. Proper treatment of chronic hepatitis C in prison is rare due to social and educational reasons and, not least, because most inmates with HCV infection remain unaware of their status, and several other barriers (drug abuse, stress, fear, lack of confidence, stigma, difficulty to relate to the health personnel) adds up to the lack of liver disease specialists in prison[142-145]. Although many prisoners are incarcerated for long periods, the average length of stay can be shorten to weeks or months in several cases, which makes it difficult to complete the clinical itinerary from screening to post-treatment follow-up[146,147].

Compared to interferon, DAA therapies are easier to roll out in community and outreach settings, but in reality there is a significant lack of experience and engagement in routine HCV screening and treatment in primary care, and misconceptions about whom to screen, risk of progression of liver disease or therapy itself in this setting[148-150]. Even specialists in liver disease may have limited experience treating HCV, or be selective about which patients they consider as good candidates for therapy and fail to recommend treatment because of concerns about nonadherence, drug use or risk of re-infection[151,152]. Furthermore, there are insufficient numbers of providers who can and are willing to treat HCV, and insufficient resources for case managers, navigators and social workers in suitable capacity to attend a growing demand of patients in need of treatment[153].

All-oral treatments are very expensive, with initial wholesale acquisition cost (WAC) of 90,000 US dollars per 3 months treatment course (or $1000/pill). While the prices of DAAs have decreased rapidly in some countries, they remain variably expensive and remain unaffordable in others[154]. In the US for example, DAA pricing is influenced by a chain of multiple organizations, including pharmaceutical companies (who determine the WAC), Pharmacy Benefit Managers (PBMs) (intermediaries between the former and health insurance companies), insurance companies (who determine the preferred choice of regimens and out-of-pocket expenses for patients), and specialty pharmacies (who receive dispensing fees and may contract with insurance companies, PBMs, or pharmaceutical companies to provide adherence support, management of adverse effects, and outcome measurements). In this system chain, negotiated drug prices are held as confidential business contracts, with no transparency regarding the actual prices paid for hepatitis C drugs. Nevertheless, the recently observed increases in WAC discounts or rebates have implied a reduction in drug costs to payers[85,155,156]. In other countries, pharmaceutical companies negotiate pricing directly with the payers (usually a nationalized system), where licensing agreements may allow for production of generic formulations and transparency in negotiated cost of drugs to payers[155,157]. Increasing generic competition has lowered DAA price, but those remain high (tens of thousands of dollars per treatment course) in developed countries, in those middle-income countries that do not have access to generic formulations, and in those countries who fall outside of license agreements. This creates a heavy financial burden on many health systems and leads to treatment rationing[154]. Comparatively, generic versions of new HCV medicines have been available for under 500 US dollars per patient in some countries, and the production cost of two DAAs could be as low as 200 US dollars per patient. Hence, further price reductions could be achieved and will be needed to increase the number of patients treated[157].

In addition to drug cost, the cost of diagnosis and disease evaluation also represent an important financial burden, especially in low to middle income countries (LMICs), which has brought uncertainty as to the opti-

mal testing approaches and who to prioritize for testing in this setting[158]. Diagnostic testing involves laboratory-based immunoassays required to meet minimum safety, quality and performance standards, and rapid diagnostic tests (RDT) with important role in settings where there is limited access to laboratory infrastructure and/or in populations where access to rapid testing would facilitate linkage to care and treatment[158]. Directly following a reactive HCV antibody serological test result, the use of quantitative or qualitative nucleid acid testing (NAT) for detection of HCV RNA is recommended as the preferred strategy to diagnose viraemic infection and monitor treatment response. An assay to detect HCV core (p22) antigen, which has comparable clinical sensitivity to NAT, is an alternative to NAT to diagnose viraemic infection[159]. According to recent WHO guidelines, focused serologic testing with HCV antibody (anti-HCV) should be offered with linkage to prevention, care and services to high-risk populations; general population testing should be approached in settings of high prevalence in the general population (2%-5% infection prevalence); and birth cohort testing should be applied to specific identified birth cohorts of older persons at higher risk of infection and morbidity within populations that have an overall lower general prevalence[158,159]. Such testing strategies, although incurring in significant cost if applied to massive testing scale-up, should still hold reasonable cost-effectiveness tailored to broad variations in gross domestic product worldwide, although there is lack of evidence among LMICs[158]. Interestingly, studies have shown that the cost-effectiveness of testing for HCV seems most sensitive to variations in prevalence, treatment efficacy, progression rates from chronic HCV to cirrhosis, and levels of linkage to care and treatment, and relatively insensitive to costs of screening and treatment[158,160-162]. Another barrier to HCV testing and evaluation scale-up is the cost involved in HCV genotype ascertainment. This is required for a number of DAA regimens available, and certainly makes the use pan-genotypic regimens an attractive cost-effective option, especially in countries with high prevalence of non-GT1 HCV, that could potentially bypass genotype confirmation[163]. Simplifying testing algorithms and lowering the cost of monitoring can dramatically cut costs of treatment for HCV in the future. For instance, the cost of the current step-wise evaluation algorithms (screening for exposure using serology or RDT; quantitative NAT testing for viremia confirmation, monitoring, efficacy assessment; and genotyping) can be as high as 220-1100 USD; whereas the cost of potential future scenarios (screening for exposure using serology, RDT, oral fluids or dried blood spots; qualitative NAT for viremia confirmation without genotyping, minimal viral load monitoring and efficacy assessment) could be as low as 15-75 USD[164].

PROGRESS IN PUBLIC HEALTH RESPONSE

Public health strategies addressing the remarkable challenges of HCV elimination has leveraged sound epidemiological data, detailed expert opinion input and mathematical modelling. In order to inform treatment and prevention strategies, as well as public health policy, efforts have focused on gathering country-specific data[165]. Collectively, evidence estimates suggest that the HCV infection burden is highly variable worldwide. For instance, the population prevalence of HCV viremia seems to range widely, from 0.3% in Austria, England, Germany and France to 7.3% in Egypt. The latter country is clearly unique, even when compared to Portugal, Brazil and the US with viremia prevalence nearing 1.0%-1.2%[166,167]. Within the estimated viremic population, there are also significant variations in the estimated rates of individuals newly diagnosed in each country (3%-14% per year) and treated (1%-11% per year)[167,168]. Liver fibrosis burden is also estimated to be greater in countries with more generalized, older epidemics such as Egypt and Brazil, in opposition to younger epidemics with large contributions of PWIDs (Australia, Czech Republic and Australia)[166]. While the overall number of new HCV infections is expected to decline worldwide, the number of cases with advanced liver disease is expected to increase[169]. This dichotomy and epidemiological contrasts between countries is fueled by high cumulative prevalence, reason why the global strategy calls for significant reductions of both the number of new infections and HCV-related mortality.

Modeling-based evidence, calibrated by country-specific epidemiological data, shows that sizable reductions in incidence, morbidity and mortality can only occur if high-efficacy therapies are combined with increased diagnosis and treatment access. Yearly treatment rates in the order of 10% are likely to position most coun-

tries on track to achieve HCV elimination targets. However, this is estimated to require a 3 to 5-fold increase in diagnosis and/or treatment rates from baseline; and robust, highly inclusive public health programs, focused on hard-to-reach populations and PWIDs[167,83]. Much progress is needed to make HCV elimination an explicit and adequately resourced public health priority, using appropriate means at all levels through collaborations between individual citizens, civil society organizations, researchers, healthcare professionals, the private sector, local and national governmental bodies[170]. Countries have been challenged to disseminate models of enhanced screening and DAA delivery in and outside tertiary care settings, such as community primary care[171], nurse-led models of care[172] and prisons[173]. Studies have demonstrated the utility of nurse-physician partnerships and training programs to improve engagement in HCV care, translated into high proportions of patients receiving counselling, education, and successful treatment with cure rates comparable to contemporary clinical trials, during the interferon and early DAA eras[171,174-176]. The results of the ASCEND trial suggested that DAAs can be independently administered by primary care physicians and nurse practitioners to challenging sub-populations, setting the foundation to HCV micro-elimination interventions such as the one carried out within the Cherokee Nation Health Services system[177,178]. HCV elimination should not be an impossible task if taken as a "think global, act local" approach, in which clinics are structured to support vulnerable populations, also in connection with harm reduction venues in the form of needle and syringe services programs (NSP) and co-location of treatment to OST clinics[179]. For example, Iceland's geographical isolation and relatively small population- comparable in size to many cities globally - makes it an important case study. In general, Iceland provide favorable conditions for geographically-targeted policies to reduce transmission among PWID (setting up testing and treatment programs, NSPs and OST in consultation with local healthcare and community service providers) without the unpredictable bias of population mobility to and from areas with varying program coverages or HCV epidemiology within the same country[180]. It is estimated that DAA scale-up to levels already being experienced, coupled with reasonable efforts to diagnose and treat PWIDs, could turn Iceland one the first countries to eliminate HCV as early as 2020[181].

The European Union (EU) rely on advanced health-care infrastructure, and is uniquely poised to eliminate HCV[182]. Estimates indicate that over one million people had been identified with positive viremic status by 2015 (36% of total viremic pool) and 133,000 were cured in 2015 alone (4% of the total infected population or 9% of the diagnosed population). The number of cures in that year was higher than the estimated number of new infections (~58,000) added to the number of HCV-infected immigrants (~30,000) believed to have entered the EU. Austria, France, Germany, Netherlands and Spain have led the way with at least 8% of infected individuals cured in 2015. But many other countries (Bulgaria, Croatia, Czech Republic, Finland, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia) have seen greater estimated numbers of new infections than the number of people cured. In order for the EU to be on track with WHO targets by 2025, unrestricted treatment still needs to increase by 25% until then, and annual new diagnosis rates by 2-fold compared to 2015 baseline[182].

In Australia, an active HCV screening program has led to 82% of HCV-infected population being diagnosed, placing the country on-track to achieve WHO elimination targets. The Australian unrestricted DAA program, launched in March 2016, adopts a fixed priced approach where the country pays a single fee for ad lib access to as much DAA therapy as it can use over a fixed period of time. This approach eliminates the "fee for service" model and instead uses a public health model that incentivizes patients and providers to employ universal screening and treat all who test positive. This has resulted in an estimated 58,500 individuals (26% of total HCV-infected population) initiating treatment through 2017. Treatment uptake has been high among sub-populations at greater HCV transmission risk (22% of PWIDs and > 60% of those with HIV/HCV coinfection initiated DAA treatment in 2016) and the country has enhanced surveillance efforts to track the program's future results. It is estimated that Australia could eliminate HCV from the continent by 2020[183].

In the United States, an estimated 260,000 people have received HCV treatment in 2015. This significant treatment volume was mostly due to large uptake of patients with advanced liver fibrosis who had been waiting for DAAs to become available[184]. Progress estimates towards elimination in the US are greatly impacted by significant increases in HCV incidence experienced from 2011 (16,000 new cases) to 2014 (31,000 new cases), largely driven by the opioid epidemic[185]. Assuming that the rates of new infection remain the same in the next 14 years, the US can only achieve WHO targets by 2030 if it expands screening to diagnose 80% of individuals infected (50% of infected individuals are diagnosed at baseline), provides unrestricted treatment for all, and maintains the number of treated patients at least 150,000 per year[184,186]. The Veterans Affairs Health System has taken on robust efforts to increase funding, negotiate reduced costs per cure, screen the majority of patients at risk, expand treatment capacity by utilizing primary care and pharmacy services and have offered unrestricted treatment to 75% their patients in need[187]. In coordination with the Center for Disease Control and Prevention and the Viral Hepatitis National Plan, multiple ongoing federal and non-federal initiatives take on similar efforts to make a dent in local HCV epidemics across the US[188].

In 2016, roughly 40,000 Egyptians died of the disease, and nearly 4.5-5 million are currently infected - the highest burden in the world for Egypt's population size[189]. Following successful negotiations between government and drug makers in 2014, DAAs have become widely available at markedly reduced prices. Since then, more than a million Egyptians have been treated[190]. In addition to lowering the cost of drugs, Egypt has succeeded in opening new treatment centers, creating electronic portals to enroll patients, and expanding its domestic pharmaceutical industry to ensure a steady pipeline of affordable medications[191].

Georgia, another country with high HCV prevalence, initiated in April 2015 the world's first program to eliminate hepatitis. With technical assistance from Centers for Disease Control and Prevention (CDC) and key partnership with drug industry to provide DAAs free of charge, the ambitious goal was defined as a 90% reduction in HCV prevalence by 2020[192,193]. From April 2015 through December 2016, a total of 27,595 persons initiated treatment for HCV infection, among whom 19,778 (71.7%) completed treatment. The number of persons initiating treatment peaked in September 2016 at 4,595 and declined during October-December. Broader implementation of interventions that increase access to HCV testing, care, and treatment for persons living with HCV are needed for Georgia to reach national targets for the elimination of HCV[194]. Brazil, with an estimated burden of 657,000 people infected, and enhanced DAA access through public health system able to negotiate 90% cost reduction in drug prices, hosted the World Viral Hepatitis Summit in 2017, and presented care cascade estimates that places the country on track of disease elimination by 2030, along with Australia, Egypt, Georgia, Germany, Iceland, Japan, the Netherlands and Qatar[195]. Taken together, these examples suggest that the largest hurdle to eliminating HCV is the cost of medications, impeding access to therapy in locations where the cost of drugs remains prohibitively expensive.

SURVEILLANCE, ADVOCACY AND POLICY GAPS

As mentioned above, political will to optimize DAA treatment access and reduce costs per cure has been a main driver for the witnessed public health progress. However, much more needs to be accomplished to ensure that the hepatitis treatment goals are reached on a global level. Currently, treatment priorities aim to improve outcomes for individuals with more advanced disease progression. This treatment prioritization aimed at the individual-level misses the opportunity to reduce incident infections at the population level through treatment as prevention aimed at individuals largely driving new infections (i.e., PWID). Treatment prioritization for those with severe liver disease is supported by cost-effectiveness analyses that exclusively accounts for individual health benefits of HCV treatment. These analyses show that treatment of moderate to severe disease is cost-effective but, at high HCV treatment costs, treatment of mild disease should be delayed[196]. However, due to the relatively long duration of HCV disease progression compared with durations of risk behavior (such as injecting drug use), treatment of those with advanced liver disease is unlikely to have prevention benefit[197]. On the other hand, models of HCV transmission that incorporate both indi-

vidual and population prevention benefit show that treating PWID could avert secondary infections (treatment as prevention) and be more cost-effective in many settings (where chronic HCV is at 40% prevalence or less among PWID) than treating other patient groups[198]. Therefore, the public response we have seen thus far creates many opportunities to reach liver mortality reduction targets by 2030, but also many challenges in reaching incidence reduction targets in the same time span. This needs to include unrestricted access to DAAs on a global scale and, in particular, enhanced HCV screening to identify the large proportion of hard-to-reach and undiagnosed individuals. Without a change in public policy that focus on reducing incident HCV infections, eradicating HCV as a pathogen will be near impossible[199]. A survey of patient advocacy groups from 25 different European Countries, has recently highlighted several specific policies and program gaps in support of elimination efforts. Although fewer countries (8 out of 25) were reported to refuse treatment to people who are currently injecting drugs in 2017, nearly half of these nations were reported to lack a national HCV strategy, and the majority of them lack key components of comprehensive strategies such as disease registries, syringe exchange programs available in all parts of the country, DAA treatment availability in non-hospital settings, and unrestricted access to DAAs[200].

Much of what is known about public health responses in HCV is based on modeling studies that are limited in their essence to be useful approximations of reality[201]. Accurate program evaluations towards disease elimination will require robust surveillance systems. Case reporting, based on regular notification by clinicians and laboratories, serological surveys and cancer and death registries are important for measuring the impact of hepatitis infections and evaluating the efficacy of interventions[202]. However, viral hepatitis surveillance shortcomings have resulted in many WHO Member States (MS) having insufficient data available to guide decision-making[203]. Among MS in the WHO European Region, key surveillance components currently exist with more than 90% of MS conducting surveillance for acute HBV and HCV infections; however, substantial systemic shortcomings were reported as well, especially in regions where the surveillance of chronic HBV and HCV infections was less common[204]. Viral hepatitis surveillance systems historically have focused on collecting data on acute infections, primarily for the purpose of identifying outbreaks, suggesting that surveillance systems may not be evolving rapidly enough to keep pace with recent developments in viral hepatitis prevention and treatment[205]. Besides, the accurate classification of viral hepatitis infection as acute versus chronic is a widely recognized challenge, especially for hepatitis C, and only a minority of MS have no hepatitis cases reported as "undifferentiated" or "unclassified"[206]. In the US, HCV surveillance has been ongoing since 1982, but the program for chronic disease surveillance is underfunded as only seven jurisdictions receive support from the CDC. Additionally, local health departments are responsible for reporting to the CDC, and the data aggregation across health departments from different governmental levels is not always accurate[207]. A greater focus on chronic disease surveillance would contribute to better understand the disease burden, assess the impact of prevention and treatment efforts, and maximize the impact of resources[208].

CONCLUSION

The advent of the DAA era sparked serious efforts towards elimination of HCV infection by 2030, which can become a reality with expanded use of DAAs. All-oral regimens have proven safe and effective in treating key HCV-infected subpopulations, including PWIDs, and allow for cure opportunities to nearly all infected patients with hepatitis C. Programmatic prospects of disease elimination will face many challenges, including: an extraordinary and ever increasing disease burden, the stigmatizing nature of the infection which challenges diagnosis, multiple societal and individual barriers to access care, and, perhaps most importantly, the high treatment costs. Unprecedented progress towards HCV elimination has been experienced in recent years, but only few countries are currently considered to be on track for disease elimination by 2030. Worldwide, countries are investigating strategies to scale-up efficient HCV screening and treatment to the levels necessary to reduce both HCV mortality and incidence. Fundamental changes in societal views, political will, surveillance and adoption of a public health treatment mindset, with sharp reduction in the cost of DAA therapy, will be required for HCV elimination worldwide.

DECLARATIONS

Authors' contributions

Design, literature research, manuscript writing: Franco RA
Manuscript editing: Galbraith JW, Overton ET
Manuscript revision: Saag MS

Availability of data and materials

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Conflicts of interest

Franco RA is has served as a consultant to Gilead and Bristol Myers-Squibb and is an investigator on grants paid to his institution from Gilead, Merck and Janssen; Galbraith JW has served on Gilead and AbbVie advisory boards and received grants from Gilead Sciences paid to his institution; Overton ET receives research support for the National Institute of Health, Gilead, Merck and Abbvie paid to his institution and has served as a consultant to Gilead and ViiV; Saag MS is a scientific advisor to Gilead, Merck, and ViiV, and principal investigator on grants paid to his institution from Gilead, Merck, and ViiV.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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