Key Elements on the Pathway to HCV Elimination: Lessons Learned From the AASLD HCV Special Interest Group 2020

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With a decade left to reach the ambitious goals for viral hepatitis elimination set out by the World Health Organization, many challenges remain. Despite the remarkable improvements in therapy for hepatitis C virus (HCV) infection, most people living with the infection remain undiagnosed, and only a fraction have received curative therapy. Accordingly, the 2020 HCV Special Interest Group symposium at the annual American Association for the Study of Liver Diseases Liver Meeting examined policies and strategies for the scale-up of HCV testing and expanded access to HCV care and treatment outside the specialty setting, including primary care and drug treatment and settings for care of persons who inject drugs and other marginalized populations at risk for HCV infection. The importance of these paradigms in elimination efforts, including micro-elimination strategies, was explored, and the session also included discussion of hepatitis C vaccine development and other strategies to reduce mortality through the use of organs from HCV-infected organ donors for HCV-negative recipients. In this review, the key concepts raised at this important symposium are summarized. (*Hepatology Communications* 2021;5:911-922).

In 2016, the World Health Organization (WHO) set goals for hepatitis C virus (HCV) elimination, defined as a 65% reduction in HCV mortality and a 80% reduction in incidence of new HCV infections by 2030.[1] The achievement of these goals can avert approximately 1.5 million deaths from HCV infection.[2] Reaching these goals will require a large scale-up of HCV testing to diagnose and treat 80% of the estimated 71 million people living with HCV.[3] HCV is an underdiagnosed and undertreated disease. Globally, by 2017, approximately 20% of HCV-infected persons were aware of their infection, and only 5 million of those diagnosed with HCV had received treatment.[4] The American Association for the Study of Liver Diseases (AASLD) convenes at least annually as a special interest group (SIG) for interested clinicians and researchers, to present and discuss the latest research in hepatitis C prevention, testing, and treatment. In the 2020 HCV SIG symposium at the annual AASLD Liver Meeting, policies and strategies were examined for the scale-up of HCV testing and expanded access to HCV care

Abbreviations: AASLD, American Association for the Study of Liver Diseases; CDC, Centers for Disease Control and Prevention; CHIM, controlled human infection model; DAA, direct-acting antiviral; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LMICs, low- and middle-income countries; OAT, opioid agonist therapy; PCP, primary care provider; PWID, persons who inject drugs; SIG, special interest group; SSP, syringe service program; SVR, sustained virologic response; VA, Veteran Affairs; WHO, World Health Organization.

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and treatment outside the specialty setting, including primary care and drug treatment and settings for care of persons who inject drugs (PWID) and other marginalized populations at risk for HCV infection. The importance of these novel paradigms for elimination efforts, including micro-elimination strategies, was explored and the session included a discussion of hepatitis C vaccine development and other strategies to reduce mortality through the use of organs from HCV-infected organ donors for HCV-negative recipients.

EXPANSION OF HCV TESTING

The WHO recommends HCV testing strategies based on local epidemiology and context. Depending on the local situation, one-time HCV testing has been recommended for the general population with HCV prevalence >2%, or ≥5%, as well as for subpopulations such as birth cohorts with a higher HCV prevalence than the populations as a whole, and for adults and adolescents at risk of exposure to HCV.[1] All persons diagnosed with HCV infection should receive treatment. To promote broad implementation, HCV testing strategies must be relatively simple, target key populations, and be readily integrated within existing health systems in resource-constrained settings. Twenty nations, mostly low-income and middle-income countries (LMICs), bear 68% of the burden of HCV-related mortality.[5]

A number of model countries are implementing highly effective HCV testing programs. Effective HCV testing programs share at least seven essential components (Table 1: (1) political and civic support; (2) a plan of action with time-limited numerical targets; (3) strategic information to guide planning and monitor program performance; (4) the capacity to deliver HCV testing services to target populations; (5) sustainable models for financing, including the negotiations of affordable diagnostics and therapies; (6) integration of HCV testing within existing health systems; and (7) operational research to improve program performance. Egypt provides an excellent example of a highly effective HCV elimination program.[6] In 2018, with catalytic funding of the World Bank, the President of Egypt set goals for HCV elimination by 2020 and called for HCV testing of all persons 18-59 years of age. The national government negotiated affordable pricing for anti-HCV (<US $1) and HCV polymerase chain reaction testing (<US $5) and for HCV medications (<US $100). The country implemented a public health approach that brings together a health promotion campaign for the public, conducts HCV testing in diverse clinical and community (e.g., mobile van) settings, and provides HCV testing and treatment at no cost to patients. In less than a year, the HCV elimination program screened 49.6 million persons, 79% of the target population, started 92% of the approximate 1.15 million with current HCV infection on treatment, and cured 98% of treated patients tested for a sustained virologic response (SVR) (Fig. 1). The program was cost-saving, with an expenditure of $131 for identifying and curing a patient with HCV. The current HCV test and treatment efforts are projected to avert more than 260,000 HCV-related deaths by 2030—a 61% decline in mortality.

TABLE 1. ESSENTIAL COMPONENTS OF HEPATITIS ELIMINATION PROGRAMS

- Data for planning and monitoring program performance
- Plan of action with time-limited numerical targets
- Civic and political support
- Capacity to deliver appropriate interventions to target populations
- Sustainable models for financing
- Integration of services within existing health systems
- Participation in operational research

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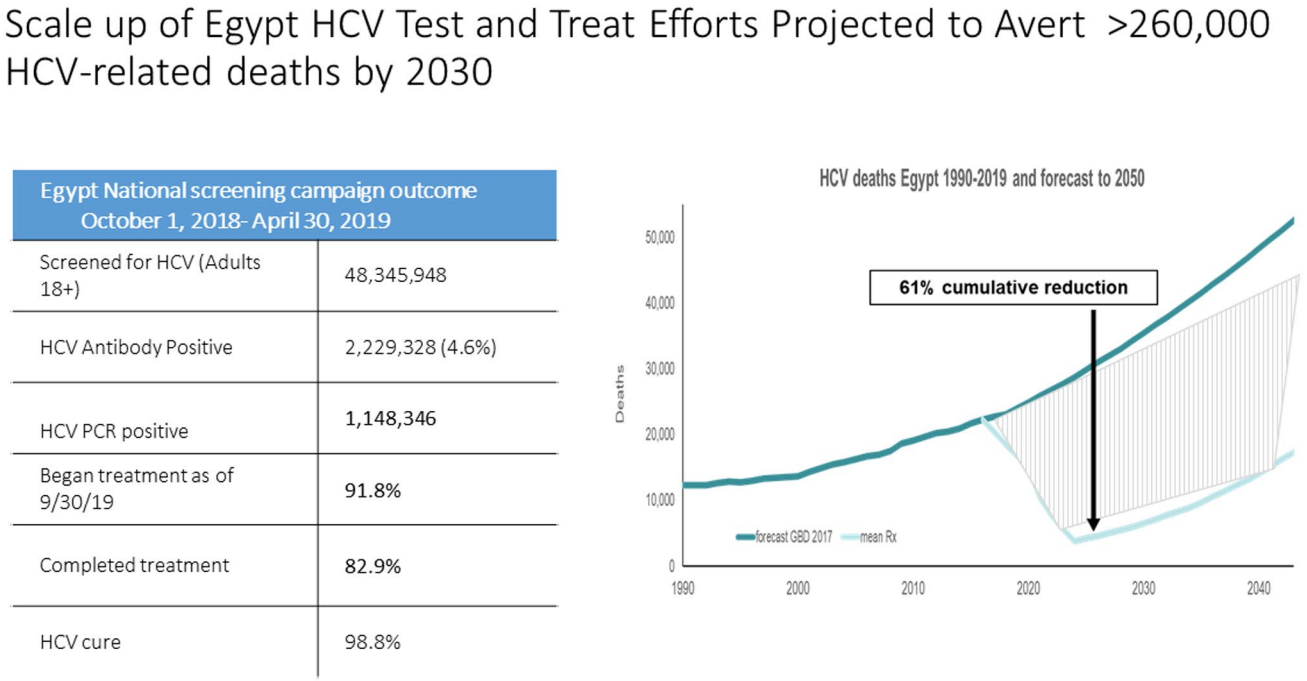

FIG. 1. Projected progress of the Egypt HCV elimination program toward meeting the goals of a 65% reduction in HCV-related mortality by 2030.

Once a major barrier to large-scale treatment, the cost of HCV therapies has declined dramatically. Indeed, currently, approximately 60% of persons infected with HCV live in countries with generic HCV medicines costing less than US $150 per course[4,7] In the United States, the cost of HCV therapies has fallen below $25,000 per course; HCV treatments costing less than $40,000 are considered cost-effective in the United States.[8,9] As a result, other countries are in various stages of implementing HCV elimination programs. Rwanda and Punjab, India, are other examples of health ministries that are scaling up HCV testing and treatment to reach goals for HCV elimination.

Most countries must overcome at least three bottlenecks to broaden access to HCV testing.[9] First, national hepatitis action plans rarely include policies to direct HCV testing for key populations. Second, the current two-step HCV testing process, HCV antibody testing followed by (if positive) a virologic test to confirm HCV infection, adds complexity and expense, and results in persons falling out of care before virologic testing is completed. Third, the availability of testing platforms is limited by costs that remain unaffordable in most LMICs or by administrative rules that preclude the use of virologic testing tools in other programs (e.g., human immunodeficiency virus [HIV], tuberculosis) for HCV testing.

TESTING POLICY IN THE UNITED STATES

HCV was discovered in 1989, leading to the development of screening tests to detect and discard blood donations from persons infected with HCV and for HCV diagnosis and care.[9] In 1998, the US Centers for Disease Control and Prevention (CDC) recommended HCV testing for persons who receive blood and blood products not screened for HCV, PWID, and others at risk for HCV infection. Epidemiologic studies that included HCV testing revealed that as a consequence of receipt of unscreened blood, and exposures to unsafe injections in health care and community settings (injection drug use), approximately two-thirds of persons infected with HCV in the United States were born between 1945 and 1965, the so-called "baby boom" generation. The development of safe and highly effective antiviral therapies for HCV

increased the benefits of HCV screening and linkage to care for persons infected with HCV. Accordingly, in 2012, the US CDC recommended a one-time HCV test for all persons born between 1945 and 1965; the following year, the US Preventive Services Task Force (USPSTF) also recommended HCV testing as a non-co-pay preventive service for this patient population.[9] The implementation of HCV testing for persons born between 1945 and 1965 improved HCV screening. From 2011-2017, HCV testing increased 139%-374% among the birth cohort, contributing to increases in HCV treatment and a decline of 24% in HCV-related mortality from 2015-2018 (Fig. 2). This mortality decline exceeds by 2-fold the 2020 interim target of >10% decline in HCV-related mortality.[7] Certain strategies facilitate implementation of birth-cohort HCV testing. The use of electronic prompt for clinicians increases by 3-fold the likelihood of clinicians ordering tests for patients recommended for HCV screening.[8] Other effective strategies include reflex RNA testing of anti-HCV+ specimens, training of clinicians to test and treat HCV infection, patient navigators to assist patients through the testing and treatment process, and access to HCV medications. The lessons learned can be applied to the scale-up of HCV testing to reach new target populations.

In 2020, the US CDC and the USPSTF recommended a one-time HCV test for all adults >18 years of age, including pregnant women.[9,10] The expansion to all adult HCV testing addresses gaps in HCV screening. Only 50% of persons infected with HCV are aware of their infection. The opioid epidemic in the United States and increases in unsafe injections during opioid use have resulted in an epidemic of HCV transmission. From 2009-2018, the incidence of HCV infection increased 3-fold to 50,300 new infections per year, primarily among persons 18-39 years of age;[11] HCV infection increased 5-fold among pregnant women. Health models show that all adult testing in the United States is cost-effective, at US $11,378-$28,000 per quality-adjusted life year. Pilot projects demonstrate the feasibility of all-adult HCV testing. In less than 2 years, the Cherokee Nation screened 51% of persons 20-69 years of age for HCV, linking 84% of persons infected with HCV to care.[12]

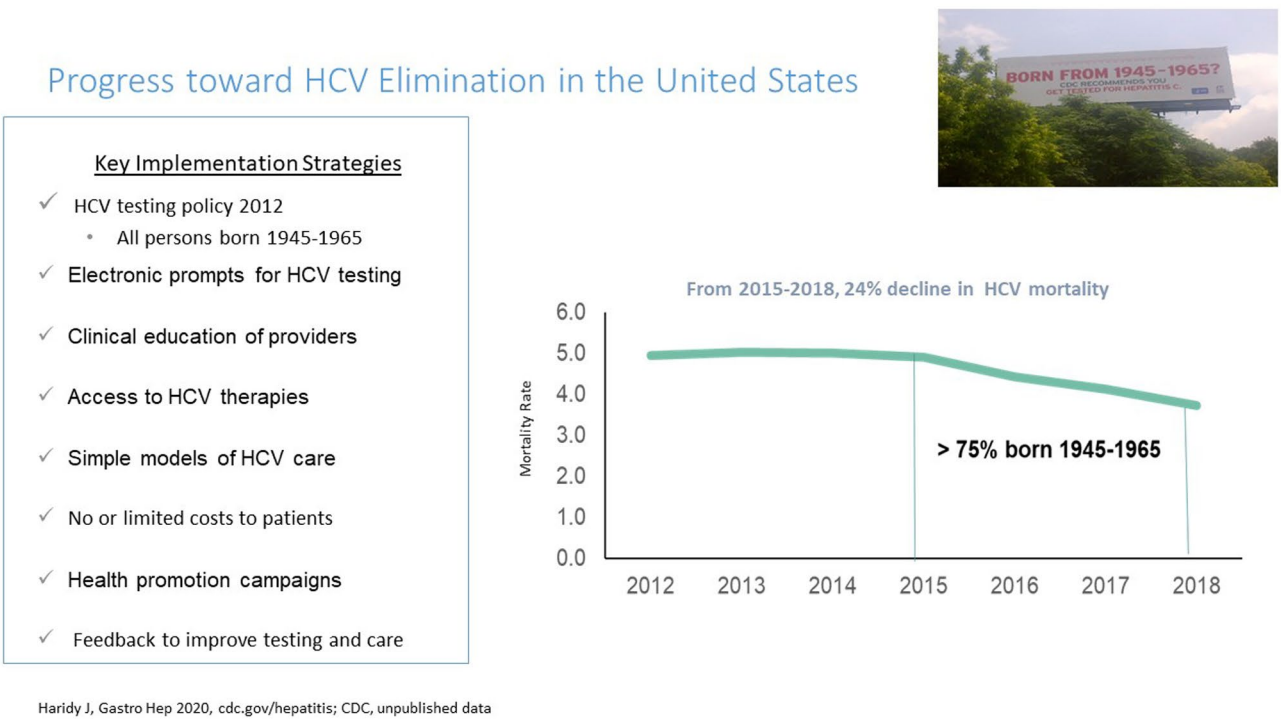

FIG. 2. With implementation of birth-cohort testing for HCV, the United States exceeded the global goal of a 10% reduction in mortality by 2030 and gained experience in expanding HCV testing to all adults.

OPTIONS FOR IMPROVING LINKAGES TO HCV CARE

To prevent disease progression and transmission, HCV testing must be followed by linkages to appropriate HCV care and treatment. Although specialty care is essential for complex cases, management of HCV care and treatment has been progressively simplified and can be readily integrated into routine primary care. Indeed, compared with referrals for specialty care, studies suggest that the proportion of patients evaluated for liver disease after an HCV diagnosis increases by several fold when the primary care provider (PCP) manages HCV testing and treatment.[11]

ESTABLISHING THE PROJECT ECHO MODEL OF TELEMENTORING NONSPECIALISTS TO TEST AND TREAT HCV

Several options are available to build the capacity of PCPs to manage HCV testing, care, and treatment. Chief among these is the Project ECHO telementoring model of linking liver-disease specialists (e.g., hepatologists, pharmacists) together with PCPs in a knowledge network to discuss the management of individual patients (i.e., case-based learning). Patients with HCV managed by PCPs in a Project ECHO network have outcomes comparable to the outcomes of patients in specialty care.[13] Project ECHO networks and ECHO-like systems, ongoing in the Americas, Africa and elsewhere, address critical gaps in availability of specialty care for patients infected with HCV in rural and underserved settings. However, time and financial constraints of PCPs can limit regular participation in the Project ECHO sessions. The response to the coronavirus disease 2019 pandemic might help address some of these challenges. For example, Medicare waivers and health systems now support clinicians using audio/video communications to provide patient care.

To improve the accessibility of the ECHO model, variations in approaches are underway, including prerecorded "immersion" workshops to help clinicians begin to treat patients for HCV, and "e-consult" and on-line clinical management tools to provide more immediate response to clinical care questions.[14-16] In San Francisco, a composite of in-person training followed by e-consult support and individualized technical assistance resulted in >100% increase in the number of patients treated for HCV infection.[15]

Colocalization of HCV Testing and Treatment in Diverse Health Care Settings

Beyond the primary care setting, colocalization of HCV care into other care sites promotes access for marginalized populations. Telemedicine, in which a clinician provides direct care to a patient, is one approach. In one study, biweekly telehealth sessions between hepatologists and clients, to guide directly observed HCV therapy at the time of methadone administration, resulted in 45 (73%) of 62 clients being evaluated and 93% of clients treated and cured of their HCV infection.[17]

Pharmacists can also manage HCV treatment for patients on opioid agonist therapy (OAT). A study in Scotland evaluated directly observed OAT and HCV treatment, provided by pharmacists, compared with the care delivered in a drug treatment center. Pharmacist-led care resulted in a 2-fold increase in HCV testing, and the start of HCV treatment.[18] This evidence strengthens the rationale for pharmacists to be a "one-stop shop" for point-of-care HIV and HCV testing, management of HCV treatment, hepatitis B virus (HBV) vaccination and OAT, and access to clean injection equipment and counseling to prevent overdoses.

Provision of Outreach Services for Marginalized Populations

Innovative programs are taking HCV testing and treatment to the street to reach homeless populations and others with unstable housing. In Los Angeles, homeless persons are offered HCV point-of-care testing, and anti-HCV+ persons are referred for treatment. In San Francisco, a Deliver Care "van" provides HCV testing and treatment with the assistance of telehealth with an experienced HCV care provider (Fig. 3). Misinformation on side effects/efficacy, the lack of secure location to keep medications, and food insecurity are some issues that arise with the launch of these innovative outreach services.

FIG. 3. University of California, San Francisco's DeLIVER Care, a mobile unit providing HCV testing and treatment PWID or who experience homelessness in San Francisco. Photo credit: @NoahBerger.

Integration of HCV Testing and Treatment With Other Services for PWID

A recommendation for HCV testing of all adults is a "safety net" option, increasing the likelihood of persons infected with HCV being screened and diagnosed early in the course of their illness. However, risk-based HCV testing as part of treatment as prevention strategies for PWID continues to be important. Globally, 8.2 million (56%) of the 15.6 million PWID have been infected with HCV, including 1.4 million PWID in North America.[19] Since 2000, the illicit use of opioids has grown rapidly in the United States, with large increases in the use of prescription opioids, followed by increased use of heroin and synthetic opioids (e.g., fentanyl). The opioid epidemic is the cause of subsequent epidemics of opioid overdoses and among persons injecting opioids, persons with HCV, and other blood-borne infections. In 2018, at least 75% of new HCV infections were related to injection drug use.[7]

Although an HCV vaccine would improve prevention effectiveness, interventions are available to dramatically interrupt HCV transmission among PWID. A combination of access to OAT, safe injection equipment for those who continue to inject, and routine testing for HCV testing and treatment can prevent 90% of new infections. Treatment and cure of HCV reduces the prevalence of HCV and the force of infection, thus reducing HCV transmission among PWID. Adherence and response to HCV therapy among PWID receiving OAT are comparable (>90% cure) to treatment outcomes for other persons infected with HCV.[20,21]

The AASLD/Infectious Diseases Society of America (IDSA) HCV Treatment Guidance recommends testing and treatment of acute and chronic

HCV in PWID, calling for substance use disorder programs and needle syringe programs to routinely offer routine, opt-out HCV antibody testing with reflex confirmatory HCV testing and linkage to care for those infected.[22] However, only 6.6% of primary care patients with injection drug user–related conditions are tested for HCV, and only 27.5% of OAT programs reported offering clients HCV screening.[23] Fortunately, many states are lessening or removing sobriety restrictions for Medicaid reimbursement of HCV treatment for PWID. Currently, 74% of state Medicaid programs impose no documented minimum time period of sobriety before authorizing HCV treatment. Increased access to HCV treatment can incentivize broader adoption of routine HCV screening for PWID.

PWID access to safe-injection equipment must also improve. The United States, with 30 exchanges per PWID per year, lags far behind the WHO goal of 200-300 needle/syringe exchanges per PWID per year considered necessary to reach HCV-elimination goals. Indeed, the number of syringe service programs (SSPs) in the United States are in short supply. In 2016, 80% of persons infected with HCV who were 18-29 years old lived farther than 10 miles from an SSP. Sustaining access to adequate SSP and OST services limits reinfection among PWID cured of their initial HIV infection.[24]

MICRO-ELIMINATION

Combining strategies for increased testing, improved linkage, and universal treatment access will be keys to reaching elimination targets. The WHO set the goal for elimination of viral hepatitis as a public health problem on a global scale, and it should remain the ultimate goal for elimination efforts. However, many have proposed the approach of so-called micro-elimination as a tool to reach the global elimination target.[25] Micro-elimination refers to elimination within a defined population. The rationale for this approach is that elimination on a smaller scale may be seen as a more tangible and realistic goal, with the idea that these serve as pilot projects for development of national programs that ultimately lead to global or macro-elimination.[26]

Populations targeted for HCV elimination vary widely (Table 2). Approaches to micro-elimination include targeting a population defined by a specific setting (e.g., prison, dialysis unit),[27] particular clinical characteristics (e.g., people living with HIV, people living with blood disorders), a health system (e.g., the Veteran Affairs [VA] health care system

TABLE 2. POPULATIONS TARGETED FOR HCV MICRO-ELIMINATION

Population	Example	Advantages	Challenges
Outreach setting	• Prison • Homeless population • Needle syringe program	• Clearly defined • Achievable • Measurable • Potential to reduce transmission	• Requires buy-in from setting (e.g., prison) • Unsustainable resources
Clinical population	• Persons living with HIV • Persons with blood disorders • Persons on dialysis/persons in drug treatment	• Well defined • Politically important	• May be difficult to measure/confirm (e.g., HIV underdiagnosis) • May be small scope • May be considered stigmatizing
Health system	• US Veterans Affairs • Health Maintenance Organization	• Access to care • Large potential impact • Achievable targets with good data systems • Model for other chronic disease management	• Need to demonstrate cost benefit • Reimbursement system
Geography	• Village/province, region	• Capitalizes on advocacy of local champions • Politically savvy • Health equity • Feasible costs • Lessons learned build support for a national initiative • Model for other chronic disease management	• Requires sustained buy-in with political and financial support • In absence of national programs, increased need for technical and financial support • Success tempered by migration from neighboring locations without an elimination program

in the United States, a health maintenance organization),[28] or a specific geography such as a village/town/state/province or even a defined nation/group (e.g., Cherokee Nation).[26,29] Clearly the scope and size of the population will affect how easily micro-elimination may be achieved; however, elimination can be impactful even on a small scale. In addition to benefiting the specific population, successful micro-elimination leads to future elimination efforts by gaining support and momentum as well as political will for future elimination efforts.[26]

There are multiple key components to any micro-elimination effort. Community engagement is critically important and should be at the center of all elimination efforts.[26] Reports from successful elimination campaigns, from the very small to the very large, universally cite the importance of strong community engagement in the design, implementation, and evaluation of the program. Clearly other stakeholders must be engaged, including funders, policy makers, and those affected by the proposed strategy (e.g., laboratory managers before a screening campaign). Data systems are critically important to be able to track success and identify areas for strategic revisions. Without strong data systems, even recognizing when elimination has been achieved may be a challenge. Other logistical supports are important to ensure that all aspects of a program are ready before it is launched. Although funding is always a challenge, strong advocacy and good data systems to demonstrate the tangible benefits of elimination can help secure funding support. Successful micro-elimination programs can be very impactful to gain political support for larger efforts. It is important that scalability be considered from early on in any elimination program, to ensure that successful pilot programs can be rolled out with much greater impact.[25]

Well-developed micro-elimination programs have been deployed in many settings, highlighting both successes and challenges. The Spanish prison system has developed multiple strategies to address the high burden of HCV among inmates. In 2015 they initiated active screening for HCV and documented a very high prevalence of 19.5% antibody positivity. By 2017, treatment was offered to 52% of those infected, and by 2018, treatment rates increased to near 100%. With high screening rates (~80%) and treatment for all, HCV-RNA prevalence fell from 11% in 2016 to 1.9% in 2019. Importantly this scale-up markedly reduced new infections, confirming the treatment-as-prevention paradigm, and led to a significant reduction in HCV-related mortality.[30] An important component of this successful micro-elimination program was the evaluation of the effects outside of the prison. By reducing transmission within the prison, impacts on HCV incidence were seen in the community at large. Remarkably, 90% of the benefits of the program were actually documented outside the prison system.[31] This observation highlights the importance of strong data collection to document the ancillary benefits of an elimination program. Ultimately, these community benefits were driving forces to maintain political and thus financial support for the prison HCV elimination program.

Multiple groups have worked to eliminate HCV among people living with HIV. There are many advantages to focusing on this relatively small but important population. In addition to the obvious health advantages for persons living with HIV, there are programmatic benefits to starting with this group. People living with HIV are usually engaged in care for follow-up of HIV, facilitating linkage to HCV testing and treatment, and thus making it easier to achieve elimination. The HIV community has been a strong health advocate with continued political and financial support for HIV control. Achieving success with HCV elimination in this co-infected population is possible and may well lead to support for broader elimination programs. Successful HCV micro-elimination efforts among people living with HIV have been rolled out in Scotland, Australia and the Netherlands, among other places.

Large integrated health systems offer the potential for micro-elimination on a fairly macro scale. The US VA health care system is an excellent example. There is a large burden of HCV in the VA system, and early on, cost concerns limited treatment uptake. However, well-coordinated leadership using excellent data systems to track success and redesign of programs in a highly iterative process ultimately led to very streamlined and efficient HCV screening and linkage to care, which put the VA on track to eliminate HCV among this enormous health care system.[28] The elimination efforts have led to tangible benefits with significant reduction in HCV-related complications, including HCC.[32] However, a key benefit to the integrated

HCV program was that engagement in HCV care also led to improved care for other related problems such as hypertension, diabetes, and heart disease among the VA population. The HCV "success story" in the VA is now used a model for identification and management of chronic disease.

Even national elimination programs may use micro-elimination to achieve more macro-elimination. Through careful evaluation of local epidemiology, countries may recognize that micro-elimination in specific populations will be key to national elimination. For example, in Iceland, recognition that the epidemic was largely focused among PWID led the country to focus its efforts on elimination in this population; partially because of the small size of the population, this effectively achieved national elimination at the same time. Alternatively, countries may implement multiple micro-elimination programs that collectively lead to national elimination. Egypt's focus on elimination in individual villages in the Nile delta is an excellent example of the effectiveness of this approach. By focusing on broad screening and universal treatment adapted to the specific needs of each individual village, the Egyptian elimination program has managed to achieve remarkable success.[33] Although similar platforms were used for each village, one might consider each its own separate micro-elimination project, which collectively lead to success at the regional and even national level. A key element to the success of the Egyptian efforts has been strong community engagement in all aspects of the program, with development of a structured and effective education program to ensure that in addition to screening and treatment, prevention efforts were developed to ensure the long-term impact of initial elimination successes.[33,34] In addition to community engagement, strong and continued political will has been a huge factor in the success of Egypt's HCV elimination efforts. Early successes in individual and small numbers of villages convinced national leaders that elimination was possible and has enabled large-scale efforts with adequate financial and political backing. The state of Punjab in India has followed a similar approach, also with great success by targeting individual villages for HCV elimination, to eventually achieve elimination in the region.

Because funding is perpetually a challenge for HCV elimination programs, creative approaches to financial support should be considered. Uzbekistan, working with the Centers for Disease Analysis, has developed an innovative model for national viral hepatitis elimination. They have proposed to have 80% of the population pay out of pocket for low-priced generic HBV and HCV treatment at slightly above cost, to enable coverage for the 20% who cannot afford to pay.[35] The government has taken on the responsibility of screening, but the program is otherwise financially self-sustaining. If this model proves successful, this could be a blueprint for elimination efforts in LMICs.

The range of structure and scale of micro-elimination projects around the world highlight the versatility of this approach. Although it is critical not to lose sight of the ultimate goal of global elimination, micro-elimination can be a very useful approach in driving progress toward the WHO global targets.

VACCINE DEVELOPMENT

It is noteworthy that the WHO has targeted elimination of viral hepatitis as a public health threat rather than global eradication. There is a clear recognition that eradication of HCV will not be achievable without a vaccine. In truth, even elimination efforts will be challenging to achieve without a vaccine, due to continued high rates of new infection, fueled by the ongoing opioid epidemic in North America and continued high incidence from drug use and unsafe medical practices in some LMICs. Data from 2017, the year with the greatest HCV treatment uptake, are disconcerting. Despite curing an impressive 1.5 million individuals, 1.6 million new infections were estimated to have occurred.[36] A vaccine will greatly facilitate changing that reality.

Vaccine development has proven extremely challenging for many reasons. The remarkable diversity of HCV is a major challenge, with even clearance of natural infection failing to provide true protection against reinfection. However, the fact that studies in chimpanzees and data from longitudinal cohorts confirm that people who clear infection once are more likely to clear again if reinfected and do so faster with a lower level of peak viremia, argue for a degree of protective immunity.[37]

In 2020, the results of the first randomized controlled trial of an HCV vaccine were presented. The

vaccine developed using a chimpanzee adenovirus vector expressing both structural and nonstructural HCV proteins was shown to generate potent immune responses with no safety concerns. The study evaluated the development of chronic HCV infection in a cohort of HCV-uninfected PWID. Unfortunately, the overall results were disappointing, with an identical proportion of both groups developing chronic HCV infection. However, the peak level of HCV RNA was 5.5-fold lower in the vaccine group, confirming at least some activity of the immunological response to the vaccine.[38] Hopefully this result will not limit further efforts at HCV vaccine development.

In addition to the major immunological challenges of developing an HCV vaccine, it is also important to consider the major logistical challenges involved in evaluating an HCV vaccine candidate. Studies of PWID or other high-risk populations are very challenging and take years to complete.[38] To accelerate the process, given the extremely high efficacy and excellent safety of direct-acting antivirals (DAAs), the concept of controlled human infection models (CHIMs), in which people are intentionally infected with HCV to study proactively the determinants of immunity and the assessment of vaccine efficacy, has been proposed. Controlled human infections have been carried out with other pathogens including dengue, malaria, and now SARS-CoV-2.[39-41] CHIM poses many ethical and scientific challenges, ranging from the specific viral inoculum to use to the duration of infection before initiation of treatment, but could prove to be an important driver of vaccine development, which would be a game-changer in the drive for HCV elimination or possibly even eradication. With or without CHIM, sustained funding and political support for vaccine development will be required to achieve success. Perceptions that HCV is a "solved problem" because of the high efficacy of DAAs may limit support for vaccine development. Only with continued reinforcement of the need for a vaccine will the support required to overcome the formidable scientific challenges to vaccine development be possible.

ORGAN TRANSPLANTATION USING ORGANS FROM HCV-POSITIVE DONORS

The success of DAAs has been the catalyst for HCV elimination efforts, but they have also opened the possibility of using organs for transplantation from HCV-infected donors, even to organ recipients without HCV. Organ shortages are a perpetual problem, leading to deaths of people on organ wait lists. The opioid epidemic and overdose crisis has led to a marked increase in the number of potential organ donors who test positive for HCV. In 2000, only 1% of all overdose donors were HCV-positive, rising to 15% by 2016 across the United States, with some states reporting rates above 30%.[42] Historically, organs from these individuals were either discarded entirely or used exclusively in people on the transplant wait list who already had HCV infection. With the near certainty of cure with DAA therapy, investigators have started to explore the use of organs from HCV-positive donors for HCV-negative recipients.

The first trials used grazoprevir/elbasvir in patients receiving kidney transplants from HCV-positive donors and showed that treatment was well-tolerated and universally successful.[43,44] Although safe in patients with renal impairment, grazoprevir/elbasvir is active in genotypes 1 and 4 only, limiting its utility, particularly given the lack of genotype information at the time of transplant in most donors. Subsequent studies focused on the use of pan-genotypic regimens to overcome this obstacle.

Multiple studies have now shown that prompt treatment with sofosbuvir/velpatasvir or glecaprevir/pibrentasvir is safe and near-universally effective. Different approaches to treatment have been evaluated, ranging from starting weeks to months following transplant to giving the first dose of treatment pre-operatively. With very early treatment, shorter durations of treatment have proven highly effective. Wooley et al. showed that immediate initiation of sofosbuvir/velpatasvir after transplant led to 100% SVR with only 4 weeks of therapy in people receiving heart or lung transplants from donors infected with HCV.[45] Feld et al. used glecaprevir/pibrentasvir with ezetimibe, as an HCV entry blocker, starting treatment 6-12 hours before transplant and continuing it for just 7 days following transplant, with 100% SVR in the 30 patients treated.[46] Shortening to less than 7 days has proven challenging with a study from Gupta et al., showing that treatment of 1 or 2 days with sofosbuvir/velpatasvir led to an unacceptably high relapse rate and some challenges with retreatment.[47]

Currently, the AASLD/IDSA recommends starting treatment immediately following transplant (or

pretransplant) using a standard duration of therapy with a pan-genotypic regimen.[22] The rationale for early treatment is based on infrequent reports of complications with delayed therapy, including HCV-related glomerulonephritis, acute fibrosing cholestatic hepatitis, and possibly higher rates of acute cellular rejection.[45,48,49] Despite the successes reported, challenges with HCV-discordant transplants remain. There is still uncertainty about the preferred regimen and optimal duration of therapy. Longer-term outcomes and any effects on graft survival have not been well documented. Logistical challenges such as coverage for DAA therapy, particularly for early (pre-discharge) treatment initiation, and ethical considerations including proper informed consent, remain challenging.

The innovations to use life-saving organs have been impactful, but it would be preferable to stem the tide of the tragic overdose deaths that have spurred the development of this therapeutic advance.

Conclusions

When viral hepatitis–elimination targets were first proposed, many felt that they were merely aspirational but not actually achievable. Remarkable progress in recent years, particularly among some leading LMICs with high HCV burden, has shown the world that HCV elimination is possible. New tools for testing, improved models for linkage, and remarkably effective therapy have led to successful national and micro-elimination programs that will ultimately lead to additional national programs and ultimately global HCV elimination. A vaccine would accelerate elimination efforts immensely and make HCV eradication achievable; therefore, it must remain a strategic priority. With a decade to go, an enormous amount of work remains to be done. The AASLD HCV SIG will continue to pursue HCV vaccine development and other innovations in prevention, testing, and treatment. The continued innovations and implementation of highly effective prevention and treatment strategies, coupled with political will and strong community engagement, are keys to achieving HCV elimination.

REFERENCES

1) World Health Organization. WHO Guidelines on Hepatitis B and C Testing. 2017. https://www.who.int/hepatitis/publications/guidelines-hepatitis-c-b-testing/en/. Accessed April 7, 2021.
2) Heffernan A, Cooke GS, Nayagam S, Thursz M, Hallett TB. Scaling up prevention and treatment towards the elimination of hepatitis C: a global mathematical model. Lancet 2019;393:1319-1329.
3) Tordrup D, Hutin Y, Stenberg K, Lauer JA, Hutton DW, Toy M, et al. Additional resource needs for viral hepatitis elimination through universal health coverage: projections in 67 low-income and middle-income countries, 2016–30. Lancet Glob Health 2019;7:e1180-e1188.
4) WHO. Progress report on HIV, viral hepatitis and sexually transmitted infections 2019. Accountability for the global health sector strategies, 2016-2021 (WHO/CDS/HIV/19.7). Geneva, Switzerland: WHO; 2019.
5) Adams A, Hiebert L, Sheena B, Dirac MA, Ward JW. Country and WHO regional trends for hepatitis C virus (HCV) mortality, 1990-2019: an analysis of the Global Burden of Disease (GBD) Study [Abstract]. Hepatology 2020;72(Suppl. 1).
6) Waked I, Esmat G, Elsharkawy A, El-Serafy M, Abdel-Razek W, Ghalab R, et al. Screening and treatment program to eliminate hepatitis C in Egypt. N Engl J Med 2020;382:1166-1174.
7) CDC. 2018 Viral Hepatitis Surveillance Report. cdc.gov/hepatitis. Accessed April 7, 2021.
8) Tsay CJ, Lim JK. Assessing the effectiveness of strategies in US birth cohort screening for hepatitis C infection. J Clin Transl Hepatol 2020;8:25-41.
9) Owens DK, Davidson KW, Krist AH, Barry MJ, Cabana M, Caughey AB, et al. Screening for hepatitis C virus infection in adolescents and adults: US preventive services task force recommendation statement. JAMA 2020;323:970.
10) Schillie S, Wester C, Osborne M, Wesolowski L, Ryerson AB. CDC recommendations for hepatitis C screening among adults—United States, 2020. MMWR Recomm Rep 2020;69:1-17.
11) Coyle C, Moorman AC, Bartholomew T, Klein G, Kwakwa H, Mehta SH, et al. The hepatitis C Virus care continuum: linkage to hepatitis C virus care and treatment among patients at an urban health network, Philadelphia, PA. Hepatology 2019;70:476-486.
12) Mera J, Williams MB, Essex W, McGrew KM, Boeckman L, Gahn D, et al. Evaluation of the Cherokee Nation hepatitis C virus elimination program in the first 22 months of implementation. JAMA Netw Open 2020;3:e2030427.
13) Arora S, Thornton K, Murata G, Deming P, Kalishman S, Dion D, et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. N Engl J Med 2011;364:2199-2207.
14) Piao C, Terrault NA, Sarkar S. Telemedicine: an evolving field in hepatology. Hepatol Commun 2019;3:716-721.
15) Faherty LJ, Rose AJ, Chappel A, Taplin C, Martineau M, Fischer SH. Assessing and expanding the evidence base for project ECHO and ECHO-like models: findings of a technical expert panel. J Gen Intern Med 2020;35:899-902.
16) Facente SN, Burk K, Eagen K, Mara ES, Smith AA, Lynch CS. New treatments have changed the game: hepatitis C treatment in primary care. Infect Dis Clin North Am 2018;32:313-322.
17) Talal AH, Andrews P, Mcleod A, Chen Y, Sylvester C, Markatou M, et al. Integrated, co-located, telemedicine-based treatment approaches for hepatitis C virus management in opioid use disorder patients on methadone. Clin Infect Dis 2019;69:323-331.
18) Radley A, de Bruin M, Inglis SK, Donnan PT, Dillon JF. Clinical effectiveness of pharmacy-led versus conventionally delivered antiviral treatment for hepatitis C in patients receiving opioid substitution therapy: a study protocol for a pragmatic cluster randomised trial. BMJ Open 2018;8:e021443.
19) Degenhardt L, Peacock A, Colledge S, Leung J, Grebely J, Vickerman P, et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and

HCV in people who inject drugs: a multistage systematic review. Lancet Glob Health 2017;5:e1192-e1207.
20) Grebely J, Hajarizadeh B, Dore GJ. Direct-acting antiviral agents for HCV infection affecting people who inject drugs. Nat Rev Gastroenterol Hepatol 2017;14:641-651.
21) Hajarizadeh B, Cunningham EB, Reid H, Law M, Dore GJ, Grebely J. Direct-acting antiviral treatment for hepatitis C among people who use or inject drugs: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2018;3:754-767.
22) Panel AIHG. HCV Guidance: Recommendations for Testing, Managing and Treating Hepatitis C. https://www.hcvguidelines.org/. Accessed April 23, 2018.
23) Bull-Otterson L, Huang YA, Zhu W, King H, Edlin BR, Hoover KW. Human immunodeficiency virus and hepatitis C virus infection testing among commercially insured persons who inject drugs, United States, 2010–2017. J Infect Dis 2020;222:940-947.
24) Canary L, Hariri S, Campbell C, Young R, Whitcomb J, Kaufman H, et al. Geographic disparities in access to syringe services programs among young persons with hepatitis C virus infection in the United States. Clin Infect Dis. 2017;65:514-517.
25) Cooke GS, Andrieux-Meyer I, Applegate TL, et al. Accelerating the elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology Commission. Lancet Gastroenterol Hepatol 2019;4:135-184.
26) Lazarus JV, Wiktor S, Colombo M, Thursz M, Foundation EIL. Micro-elimination—a path to global elimination of hepatitis C. J Hepatol 2017;67:665-666.
27) Crespo J, Llerena S, Cobo C, Cabezas J. Is HCV elimination possible in prison? Rev Esp Sanid Penit 2017;19:70-73.
28) Park A, Gonzalez R, Chartier M, et al. Screening and treating hepatitis C in the VA: achieving excellence using lean and system redesign. Fed Pract 2018;35:24-29.
29) Mera J, Vellozzi C, Hariri S, Carabin H, Drevets DA, Miller A, et al. Identification and clinical management of persons with chronic hepatitis C virus infection—Cherokee Nation, 2012-2015. MMWR Morb Mortal Wkly Rep 2016;65:461-466.
30) Cabezas J, Castrejon OM, Acín E, Gonzalez FF, Aznar CM, Mateo M, et al. Hepatitis C infection in the Spanish prison system. Elimination is a dream at our fingertips. J Hepatol 2020;73:S33.
31) Dalgic OO, Samur S, Spaulding AC, Llerena S, Cobo C, Ayer T, et al. Improved health outcomes from hepatitis C treatment scale-up in Spain's prisons: a cost-effectiveness study. Sci Rep. 2019;9:16849.
32) Beste LA, Green P, Berry K, Belperio P, Ioannou GN. Hepatitis C–related hepatocellular carcinoma incidence in the Veterans Health Administration after introduction of direct-acting antivirals. JAMA 2020;324:1003-1005.
33) Shiha G, Soliman R, Mikhail N, Easterbrook P. Educate, test and treat model towards elimination of hepatitis C infection in Egypt: feasibility and effectiveness in 73 villages. J Hepatol 2020;72:658-669.
34) Shiha G, Metwally AM, Soliman R, Elbasiony M, Mikhail NNH, Easterbrook P. An educate, test, and treat programme towards elimination of hepatitis C infection in Egypt: a community-based demonstration project. Lancet Gastroenterol Hepatol 2018;3:778-789.
35) Dunn R, Musabaev E, Razavi H, Sadirova S, Bakieva S, Razavi-Shearer K, et al. Progress toward hepatitis B and hepatitis C elimination using a catalytic funding model—Tashkent, Uzbekistan, December 6, 2019-March 15, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1161-1165.
36) Hill AM, Nath S, Simmons B. The road to elimination of hepatitis C: analysis of cures versus new infections in 91 countries. J Virus Erad 2017;3:117-123.
37) Bailey JR, Barnes E, Cox AL. Approaches, progress, and challenges to hepatitis C vaccine development. Gastroenterology 2019;156:418-430.
38) Page K, Melia M, Vennhuis RT, Winter M, Rousseau KE, Massaccesi G, et al. Randomized Trial of a Vaccine Regimen to Prevent Chronic HCV Infection. N Engl J Med 2021;384:541-549.
39) Roestenberg M, Mo A, Kremsner PG, Yazdanbakhsh M. Controlled human infections: a report from the controlled human infection models workshop, Leiden University Medical Centre 4–6 May 2016. Vaccine 2017;35:7070-7076.
40) Whitehorn J, Van VC, Simmons CP. Dengue human infection models supporting drug development. J Infect Dis. 2014;209(Suppl. 2):S66-S70.
41) Spring M, Polhemus M, Ockenhouse C. Controlled human malaria infection. J Infect Dis 2014;209(Suppl. 2):S40-S45.
42) Durand CM, Bowring MG, Thomas AG, Kucirka LM, Massie AB, Cameron A, et al. The drug overdose epidemic and deceased-donor transplantation in the united states: a national registry study. Ann Intern Med 2018;168:702-711.
43) Goldberg DS, Abt PL, Blumberg EA, Van Deerlin VM, Levine M, Reddy KR, et al. Trial of transplantation of HCV-infected kidneys into uninfected recipients. N Engl J Med. 2017;376:2394-2395.
44) Durand CM, Bowring MG, Brown DM, Chattergoon MA, Massaccesi G, Bair N, et al. Direct-acting antiviral prophylaxis in kidney transplantation from hepatitis C virus-infected donors to noninfected recipients: an open-label nonrandomized trial. Ann Intern Med. 2018;168:533-540.
45) Woolley AE, Singh SK, Goldberg HJ, Mallidi HR, Givertz MM, Mehra MR, et al. Heart and lung transplants from HCV-infected donors to uninfected recipients. N Engl J Med. 2019;380:1606-1617.
46) Feld JJ, Cypel M, Kumar D, Dahari H, Pinto Ribeiro RV, Marks N, et al. Short-course, direct-acting antivirals and ezetimibe to prevent HCV infection in recipients of organs from HCV-infected donors: a phase 3, single-centre, open-label study. Lancet Gastroenterol Hepatol 2020;5:649-657.
47) Gupta G, Yakubu I, Bhati CS, Zhang Y, Kang LE, Patterson JA, et al. Ultra-short duration direct acting anti-viral prophylaxis to prevent virus transmission from hepatitis C viremic donors to hepatitis c negative kidney transplant recipients. Am J Transplant 2020;20:739-751.
48) Cypel M, Feld JJ, Galasso M, Pinto Ribeiro RV, Marks N, Kuczynski M, et al. Prevention of viral transmission during lung transplantation with hepatitis C-viraemic donors: an open-label, single-centre, pilot trial. Lancet Respir Med 2020;8:192-201.
49) Molnar MZ, Nair S, Cseprekal O, Yazawa M, Talwar M, Balaraman V, et al. Transplantation of kidneys from hepatitis C-infected donors to hepatitis C-negative recipients: single center experience. Am J Transplant 2019;19:3046-3057.