Hepatitis C Virus Elimination in the United States: Challenges, Progress, and Future Steps

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Abstract: Hepatitis C virus (HCV) infection is a major public health challenge with a simple, highly efficacious, all-oral therapy (direct-acting antivirals) that can achieve cure. Owing to the ease of treatment, the World Health Organization outlined goals to eliminate HCV by the year 2030. However, unforeseen challenges have hampered progress, and few countries are on track to meet these goals. Significant disparities remain among priority populations because of barriers to care on the systemic, provider, and patient levels. In turn, many local, state, and national organizations have been persistent in tackling these barriers, the greatest of which is linkage to care. In 2023, the White House launched a multipronged national initiative to eliminate HCV infection. The resulting economic impact of the national HCV elimination program is estimated to yield a significant net cost savings of $18.1 billion within a 10-year period. This article addresses the barriers to HCV care in different priority populations and discusses innovative models of HCV care that have been introduced in the United States.

Keywords
Hepatitis C, health equity, direct-acting antivirals, elimination, public health

Since its discovery in 1989, hepatitis C virus (HCV) has surpassed HIV as a leading cause of death by an infectious disease with an estimated 1.5 million new cases per year and nearly 290,000 deaths per year and 58 million people worldwide living with chronic HCV infection.[1,2] Within 3 years of the discovery of this RNA virus, public safety measures were implemented to reduce transfusion-associated transmission, and approved therapies emerged starting with injectable interferon-alpha monotherapy, soon to be replaced by pegylated interferon and ribavirin.[3] This high-toxicity regimen was considered standard of care between 2001 and 2011 until the introduction of the more potent, well-tolerated, oral direct-acting antivirals (DAAs) with simplified, shorter regimens in the form of a single pill such as sofosbuvir/velpatasvir (Epclusa, Gilead) and glecaprevir/pibrentasvir (Mavyret, AbbVie).[4,5] With better efficacy and adherence, DAAs improved cure rates up to 95% of people, revolutionizing the global HCV crisis into a curable disease.

The number of new cases in the United States nearly quadrupled between 2011 and 2019, coinciding with the opioid crisis; however, the

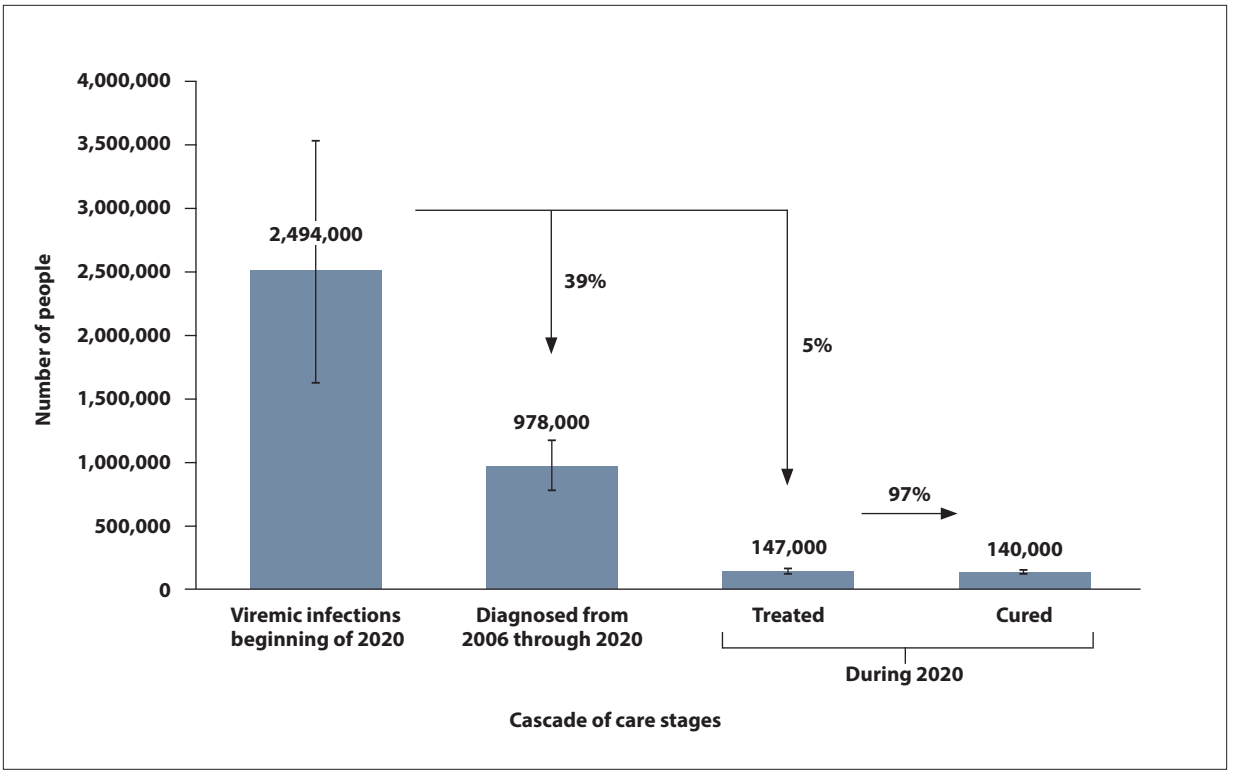

Figure. Cascade of HCV infections in the United States during 2020 shows a decline from the estimated number of HCV infections diagnosed (39%) and treated (5%).

HCV, hepatitis C virus. Reproduced from Blach S et al.[14]

number of annual deaths has also significantly declined in recent years with the development of new therapies and public health policies in screening, diagnosis, and treatment.[6-8] Although acute HCV infections can spontaneously resolve, a significant proportion of them become chronic infections, increasing the risk of progression to cirrhosis and hepatocellular carcinoma (HCC).

There has been little success in the development of an effective vaccine against HCV, which is a multifaceted problem owing to its genetic diversity and other biological, financial, and logistical challenges.[9] In particular, the hypervariable region of the HCV envelope proteins protects the virus from the host immune system and currently is insurmountable in vaccine development. In a recent clinical trial funded by the National Institute of Allergy and Infectious Diseases, the experimental recombinant prime-boost AdCh3NSmut1/MVA-NSmut vaccine failed to show prevention for chronic HCV infection.[10] Realistically, an HCV vaccine will not likely become available in the foreseeable future. This is one of the challenges to HCV elimination discussed in this article, which also covers progress in testing and preventing transmission as well as future steps to improve care and cure of this disease in the United States.

Report Card of Hepatitis C Elimination in the United States

In 2016, the World Health Organization (WHO) adopted a global health sector strategy to eliminate viral hepatitis by 2030 through 4 goals: (1) diagnosing 90% of all HCV-infected populations, (2) reducing new cases of chronic HCV by 80%, (3) treating 80% of eligible HCV-infected individuals, and (4) reducing HCV-related deaths by 65%.[11] The WHO 2022 guidelines outlined several key recommendations to optimize inclusivity and accessibility, including shifting focus to screening and treatment of vulnerable populations beyond the primary care office, simplified diagnostic testing, and expanding treatment to children and adolescents.[12] Additionally, in 2020 the Centers for Disease Control and Prevention (CDC) in accordance with the Infectious Diseases Society of America (IDSA) and American Association for the Study of Liver Diseases (AASLD) recommended universal HCV screening in all adults ages 18 years and older and pregnant women in addition to people with risk factors; the United States Preventive Services Task Force (USPSTF) came out with similar guidelines with a minor difference specifying ages 18 to 79 years.[13] Despite

emphasis on universal screening, there continues to be significant drop-off along the HCV infection cascade to cure (Figure).[14] In addition, there have been significant cascading impacts to this initiative by the COVID-19 pandemic.[15,16] A recent survey showed 80% of high-income countries, including the United States, are not on track to meet this goal of universal screening.[15]

To get the United States on track to meeting the WHO elimination goals, the Biden-Harris administration has launched a 5-year national initiative to eliminate HCV in over 2.4 million individuals.[17] This plan is estimated to cost approximately $12.3 billion and will result in shifting current funds from the Medicaid program for hepatitis C medications. A recent analysis found the national HCV elimination plan will lead to a reduction in 24,000 deaths from HCV-related disease, add 220,000 life-years, and result in a net cost savings of approximately $18.1 billion within 10 years, which is expected to increase by more than 2-fold over 20 years.[18]

Testing Strategies

The evolution of HCV testing in the United States has reflected the shifts in epidemiology and disease management over the years. Prior to 2012, HCV testing was recommended for at-risk populations, including persons who inject drugs (PWIDs), recipients of blood transfusions or organ transplant prior to 1992, and infants born to mothers who tested positive for HCV infection.[19] Risk factors were identified by patient interviews, and it was well-known that approximately half of HCV cases were missed by this method. In 2012, the guidelines were amended to include universal screening of the baby boomer cohort born between 1945 and 1965 as many infections were missed in this population.[19] Simultaneously, the opioid crisis began to unfold across the United States. This led to a new rise of HCV cases among young PWIDs, resulting in a new bimodal age distribution in HCV cases.[19] At the same time, the emergence of DAAs drastically changed the course of disease progression and curability of the disease. In accordance with the HCV elimination goal set by the WHO in 2016, the CDC/IDSA/AASLD and USPSTF guidelines in March and April of 2020 were updated to recommend universal one-time screening for all adults 18 years and older and all pregnant women during each pregnancy in addition to screening on an as-needed basis for adults in at-risk groups.[13]

The introduction of universal screening was a critical step toward eliminating HCV, and a variety of strategies have been implemented to achieve this with varying success. The goal is to simplify patient care pathways by optimizing accessibility and ease of testing for both providers and patients, streamlining coordination of care, and reducing cost burden. Since May 2013, the CDC has recommended an initial screening with HCV antibody, either rapid or laboratory-conducted assay; if positive, additional testing with reflexive HCV RNA assay, commonly known as nucleic acid testing or nucleic acid amplification testing (NAAT), is required to differentiate active vs resolved infection.[20]

Critical entry points to the HCV care pathway need improved access. For instance, HCV testing could be simplified if an HCV antibody and a viral load were not required, and instead a point-of-care (POC) HCV viral load or HCV core antigen test or assay was available. Currently, POC HCV RNA or HCV antigen assays are not approved by the US Food and Drug Administration (FDA) for diagnostic purposes in the United States.[21] POC HCV viral load testing has been shown to have high sensitivity of 100% and high specificity of 97% when compared with traditional laboratory-based testing and has shown shortened time from diagnosis to treatment and uptake in treatment.[22,23] A qualitative substudy of the PIVOT study in Australia looking at patient acceptability of POC HCV RNA testing in a prison population showed satisfaction with the ease and quick results of POC testing.[24] Officially recommended by the WHO, POC testing is the preferred assay for marginalized and hard-to-reach populations, as it can be easily distributed to and facilitated by nonspecialist providers and nurses to a variety of locations (clinics, mobile units, and prisons) and allows for same-day diagnosis and treatment.[7,22]

Once diagnosis has been made, patients must be linked to a health care provider who can evaluate and treat HCV infection. To facilitate this, the AASLD-IDSA simplified guidelines were published with a special focus on making HCV treatment accessible to all providers, not just hepatologists and infectious disease specialists.[25] A few community-based programs have coordinated HCV screening and designed innovative linkage-to-care interventions, showing promise in their local communities.[26] One of many programs that aim to address at-risk populations is the University of California San Francisco's DeLIVER Care mobile clinic. The mobile clinic's liver care team goes directly to sites where HCV infection is highly prevalent, such as safe syringe sites, methadone clinics, and community events, weekly to provide HCV testing, laboratory draws, opportunities to meet with HCV clinicians, fibrosis scans, and medications.[27] During the COVID-19 pandemic, a grassroots initiative, End Hep C SF, in San Francisco took the opportunity to offer HCV screening and linkage to care whenever there were COVID-19–related events in single-room occupancy or shelter-in-place hotels.[28]

Within larger health care systems, programs that develop a standardized method of addressing multiple

steps in the HCV care cascade show improved outcomes. Kaiser Permanente Mid-Atlantic States trialed an HCV-specific program comparing a standardized, coordinator-supported approach (HCV pathway) with usual, nonstandardized care from 2015 to 2018, which showed a statistically favorable difference in certain milestones such as completion of hepatic transient elastography, first gastroenterology visit, and prescription filled for treatment.[29] As the United States looks to improve HCV screening and linkage-to-care interventions, reducing the financial burden of testing and treatment will also be crucial. Another example of HCV elimination within a large health care system is the US Department of Veteran Affairs, which has resulted in cure rates of at least 90% owing to strong infrastructure involving multidisciplinary HCV teams in addition to reduced drug prices for DAAs.[30]

Preventing Transmission

HCV is transmitted through contact with infectious blood or blood-derived bodily fluid, and the risk factors include organ/tissue transplantation and blood transfusions before 1992 from infected donors, injection drug use, sex with infected partners, vertical transmission from infected mother to baby and, rarely, health care exposure.[31] Prior to the official discovery of HCV, blood transfusion–associated non-A, non-B hepatitis occurred in 1 in 50 units of blood transfused because of unsafe, contaminated practices (eg, poorly sterilized equipment, lack of donor screening).[32] The repercussions of these practices resulted in an estimated 10% to 20% of cases of transfusion-associated HCV infection, those of which carry the same risk of progression to cirrhosis, end-stage liver disease, and HCC.[33,34] In the late 1980s as non-A, non-B transfusion-related hepatitis began to be recognized, blood collection agencies started donor screening with surrogate markers. The discovery of HCV prompted the development and adoption of enzyme immunoassays for HCV antibody screening in 1990, which were used in combination with NAAT for its quicker turnaround time and discernment of the stages of HCV infection, although some risk still exists given the window period of infection when RNA viral load is not yet detectable.[34,35] In combination with virus inactivation techniques, the current risk of transmission has considerably decreased to approximately 1 in every 1 million units transfused.[34]

As opposed to the near-elimination of transfusion-associated HCV, vertical transmission from mothers infected with HCV to their newborns remains to be solved. The reason for this is largely because of the lack of viable treatment for pregnant mothers and poorly understood pathogenesis during pregnancy. The TiP-HepC (Treatment in Pregnancy for Hepatitis C) registry is an ongoing retrospective study looking at mother-infant outcomes after exposure to DAAs.[36] Currently, there is a multicenter clinical trial in phase 4 evaluating treatment of HCV infection during pregnancy with sofosbuvir/velpatasvir; however, as it stands, the official recommendation is to avoid perinatal treatment owing to unknown consequences of available medication on the pregnancy.

The risk of HCV transmission during pregnancy is estimated at 3% to 10%, although it may be considered an underestimate given that screening guidelines changed in 2020 and testing strategies vary, meaning some infections may clear before testing.[37] Risk factors such as HIV coinfection, premature rupture of membranes, and maternal viral load are well known. Mode of delivery, breastfeeding, and amniocentesis have not been shown to be associated risk factors for HCV transmission to the newborn.[37] The American Academy of Pediatrics, IDSA, and AASLD recommend screening for HCV antibodies at age 18 months, and again at age 3 years for chronic HCV infection with confirmatory HCV RNA testing.

Currently, treatment is not approved for children younger than 3 years owing to a lack of safety data in this population.[6] Prior to 18 months while awaiting clearance of maternal passive antibodies, HCV RNA can be tested in the first year of life with 2 serum samples 3 months apart (typically at 3 months and 6 months of age). Treatment of children aged 3 years and older is an option owing to the FDA-approved regimens for this population, is cost-effective, and has been shown to reduce long-term complications of chronic HCV.[38] The FDA-approved DAAs for children and adolescents in this age group are glecaprevir/pibrentasvir, sofosbuvir/velpatasvir, and ledipasvir/sofosbuvir.

Strategies to Improve Care and Cure

Despite the advancements in public health measures in reducing HCV transmission, there has been an increase in incidence of HCV cases in certain populations owing to injection drug use, especially in the wake of the opioid crisis.

Persons Who Inject Drugs

From the era of the baby boomer to now, the leading risk factor for acquiring HCV infection in the United States has been intravenous drug use. With the onset of the opioid epidemic, the incidence of HCV infection among PWIDs increased more than 2-fold from 2004 to 2014. This group also has a higher prevalence of HCV infection of approximately 50% to 80% when compared with 1.1% of the general US population and 3.25% of those born between 1945 and 1965.[39,40] With low HCV treatment uptake among PWIDs, it becomes crucial to

Table. Barriers to HCV Screening and Linkage to Care[41]

Patient
• Lack of access to care • Comorbid conditions (eg, mental illness, substance abuse) • Instability (eg, housing concerns, unemployment) • Asymptomatic disease • Other factors: poor education, fear of treatment, stigma
Provider
• Time constraints or insufficient number of providers • Limited knowledge about HCV and screening recommendations • Unwillingness/low priority to manage HCV infection • Unaware of current treatment guidelines
Health Care System
• Multistep process for testing, diagnosis, linkage to care • Need for support services (case managers, navigators, social workers) • Limited accessibility of HCV care locations • Multistop referral pathway and segregated service delivery

HCV, hepatitis C virus.

address the system-level, provider-level, and patient-level barriers to care (Table).[41]

Directing resources toward harm reduction services for PWIDs helps target specific faults in the care pathway such as insufficient testing, low initiation rates of therapy, high reinfection rates, and inadequate access to harm reduction resources. Harm reduction services should target the socioeconomic factors behind these behaviors. Such services may include sterile syringe access programs, opioid agonist treatments, and supervised injection sites for illicit drug use. Decentralization and integration through community-based programs can reduce stigma and marginalization. In addition, addressing the housing crisis and problems with Medicaid/insurance coverage can increase adherence to treatment.[42-44]

One novel randomized, multicenter study addressed 2 different patient-centered models in PWIDs and found both models of modified directly observed therapy and patient navigation to have high sustained virologic response.[45] A hepatitis academic mentoring partnership between primary care and specialists was established in West Virginia, which resulted in a 98.6% cure rate with no differences in cure rates between the providers.[46] Another study of PWIDs in an urban center in Baltimore, Maryland revealed a higher rate of linkage to HCV care if patients were already enrolled in an opioid treatment program.[47] Prior to the launch of the Hepatitis C: State of Medicaid Access project 6 years ago, a majority of states required prior authorizations for hepatitis C treatment; however, there is currently a growing trend toward removal of these prior authorization requirements.[48]

HIV and Hepatitis C Virus Coinfection

Per the CDC, there are approximately 1.2 million people living with HIV in the United States and of this population, 21% have HIV/HCV coinfection.[49] This subgroup has had a higher rate of hepatic-related morbidity and mortality, nonhepatic organ dysfunction, and overall mortality than people with HCV alone.[50,51] The rate of reinfection is even higher at 25% to 33% within 2 years among people coinfected with HIV/HCV after achieving sustained virologic response.[52]

Part of the reason for such high prevalence in this population may be the many barriers to obtaining HCV therapy. A study of the HCV cascade of care at an HIV clinic in San Diego, California found several barriers to seeking treatment, including unstable housing, having AIDs, having a detectable HIV viral load, and being non-White.[53] As such, it becomes imperative to initiate treatment for chronic HCV infection in people with HIV.

Instead of the traditional paradigm of referring patients to a hepatologist for HCV services, an effective multidisciplinary model is demonstrated by the integrated HIV/HCV clinic at Brown University School of Medicine in Providence, Rhode Island.[54] In this clinic, there is an on-site HIV specialist, hepatologist, coinfection nursing staff, and clinic coordinator in addition to partnerships with local community mental health agencies in providing psychiatric care and referrals for addiction treatment. Additionally, methadone treatment programs can serve as an opportunity to provide these interdisciplinary services. For instance, the Division of Substance Abuse at Albert Einstein College of Medicine in Bronx, New York, has a full-time physician board certified in internal medicine or family medicine who also serves as an inpatient attending for clinic patients who are hospitalized. The physician in addition to a physician assistant, psychiatrist, social worker, nursing staff, and substance abuse treatment counselors all work together to provide general and HIV-related medical, substance abuse, and mental health services.[55]

Incarcerated Individuals

Of the estimated 10.2 million people who have been in prison since 2015, at least 30% of those have had HCV infection at some point in time, with a seroprevalence rate reported to be higher in the incarcerated population than the overall US population.[39,56] Per the Federal Bureau of Prisons' recommendations, all inmates are screened at least once with HCV antibody testing, but there is an option for inmates to opt out of voluntary HCV test-

ing on admission, and for those who are found to have chronic HCV infection, there is further evaluation for liver disease.[57] Given the transient nature of the incarcerated population and short average incarceration period of days to weeks, it is worth pursuing a more individualized approach to screening and treating groups depending on their length of stay; this should be seen as an opportunity to screen these populations in a supervised environment.[58] An example of this customization is shown by the Virginia Department of Corrections (DOC), in which initially incarcerated persons upon entrance receive opt-out testing, opt-in testing is offered near their release date, and repeat testing can be requested at any point during their sentence.[59] The University of Virginia teamed up with the Virginia DOC in 2019 to support individuals recently released from prison who were diagnosed with HCV infection or had previous exposure to HCV by providing another opportunity to pursue treatment if this was not completed during their prison sentence.[60] Strategies to engage these patients following their release from prison are through outreach mobile clinics, drug rehabilitation, and needle exchange programs.[61]

A cost-effectiveness analysis found that the most cost-effective method to addressing the HCV prevalence in the incarcerated population is to "test all, treat all, with linkage at release."[62] However, one of the biggest barriers to this strategy is the budgetary cost in the first year, which would amount to an estimated $11.5 million, which is an expensive endeavor for prisons. To overcome this financial barrier, the Louisiana DOC collaborated with the Louisiana Department of Health, the Bureau of Health Services Financing (Medicaid), and the Office of Public Health in developing an innovative subscription program for Louisiana incarcerated persons and those on Medicaid known as the Netflix subscription model. Medicaid and the DOC will pay a fixed rate to the Louisiana Department of Health and Asegua Therapeutics—a Gilead Sciences subsidiary—for an unlimited amount of HCV medication (sofosbuvir/velpatasvir) as part of a 5-year agreement with the goal of treating at least 31,000 HCV-positive patients by 2024.[63]

Indigenous Populations

Since 1995, there has been a significant disparity in the reporting of HCV prevalence of indigenous populations, and wide ranges of HCV prevalence of American Indian/Alaska Native (1.49%-67.60%) and indigenous populations (2.28%-90.24%) reported in the literature.[64] Regardless, this population is estimated to have the highest incidence and at least a 2-fold rate of HCV-related mortality compared with the general population.[65] In response to such a high mortality rate, one of the largest health care providers for this population, the Indian Health System, launched a telementoring support system in 6 states (Washington, Oregon, Idaho, Montana, North Dakota, and South Dakota) in 2018 called ECHO (Extension for Community Healthcare Outcomes). ECHO was established to help connect rural clinicians to specialists in HCV treatment, resulting in over 70% of participating sites prescribing DAAs.[66] A large cohort study found that sofosbuvir-based regimens resulted in an overall high sustained virologic response of 97.3% in the American Indian/Alaska Native population that sought treatment at an Alaska Native medical center.[67]

With cost in mind, specific Indian health systems (eg, the United Indian Health Services [UIHS] in Northern California and Klamath Tribal Health & Family Services in Oregon) have been proactive in recommending that all eligible patients sign up for third-party resources, such as Centers for Medicare and Medicaid Services and private insurance, and patient assistance programs for financial waivers. By far, one of the many successful Indian health systems that will meet its target of eliminating more than 95% of active HCV infection cases by 2024 is the UIHS, a rural primary care network with high HCV prevalence. Its success is a result of multiple factors in addition to the elements mentioned previously and includes having a medication-assisted treatment for opiate use disorder, opting for video/phone visits instead of in-person visits to limit transportation burden, harm reduction services, a solid patient navigation system, and insurance-covered treatment.[68]

Hepatitis C Virus–Infected Pregnant Women

From 2009 to 2014, the rate of HCV infection during pregnancy increased from 1.8 to 5.1 per 1000, while mother-to-child transmission of HCV occurred in 5.8% of pregnancies and doubled to 10.8% with HIV coinfection.[69] The current USPSTF guidelines recommend all pregnant women to be screened each pregnancy except for low prevalence settings of less than 0.1%.[70] Currently, there are no recommended FDA-approved HCV treatments for pregnant women and according to the Society of Maternal-Fetal Medicine guidelines, only DAAs can be used in clinical trials or during the postpartum period after breastfeeding.[71]

As such, the peripartum period presents an optimal time to screen for HCV infection because many states provide insurance coverage through Medicaid and compliance for further testing tends to decrease following delivery.[72,73] A novel study done at Boston Medical Center in Boston, Massachusetts examined maternal-infant linkage to care and multidisciplinary substance use interventions in peripartum women and found 2 times the rate of HCV treatment initiation with just linkage to care and 3 times the rate of HCV treatment initiation with both

linkages to care and multidisciplinary substance use interventions.[74] Also in this same study, 90% of peripartum women infected with HCV were found to have a current or prior history of opioid use disorder, which strongly supports the need to integrate addiction medicine into HCV care.[75]

Conclusion

Despite the advances in the United States regarding diagnosis and treatment of HCV infection, the country is not on track to meeting the 2030 goals for HCV elimination owing to continued barriers at the systemic, provider, and patient levels. With the recent announcement from the White House to galvanize HCV elimination efforts, there is hope that strong central leadership will lead to the containment of DAA therapy costs and the loosening of prescription restrictions. The formal national policy should also help enhance collaboration among different communities in the care of priority populations for HCV elimination by 2030.

Disclosures

Dr Nguyen and Dr Moussa have no relevant conflicts of interest to disclose. Dr Gutierrez is a speaker and advisor for AbbVie, Alexion, Exelixis, and Gilead Sciences; he is also a consultant for HepaTx, Livios, and Altimmune.

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