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INFECTIOUS DISEASE EPIDEMIOLOGY (A REINGOLD, SECTION EDITOR)

Hepatitis C: Review of the Epidemiology, Clinical Care, and Continued Challenges in the Direct-Acting Antiviral Era

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Abstract
Purpose of Review This review highlights key studies and recently published data, policies, and recommendations related to hepatitis C virus (HCV) epidemiology, transmission, and treatment.
Recent Findings HCV is a leading cause of liver-related deaths, cirrhosis, and hepatocellular carcinoma. Since 2011 and accelerating since 2013, new, safe, tolerable, and curative therapies have considerably altered clinical and public health frameworks related to the prevention, control, and clinical management of HCV. Nevertheless, there are several populations in the USA that are important to consider because of disparities in HCV prevalence and transmission risk. Adults born during 1945–1965 have an estimated anti-HCV antibody prevalence of ~3%, which is six times higher than among other adults, are often unaware of their infections, and are at increased risk of having HCV-associated morbidity and mortality from decades of chronic infection. Since the early 2000s, increasing incidence of acute HCV infections among young, white, non-urban people who inject drugs has been reported. Despite promising therapeutic advances, significant challenges remain for reducing HCV-associated morbidity and mortality.
Summary The high burden of HCV and significant health consequences associated with chronic infection make HCV a critical public health priority. Advances in HCV treatment have created new opportunities for reducing HCV-associated morbidity and mortality. These treatments are safe, well tolerated, and highly effective; however, benefits cannot be realized without a significant increase in the number of persons tested for HCV so that all chronically infected individuals can be aware of their diagnosis and linked to appropriate clinical care.

Keywords Hepatitis C · Injection drug use · Baby boomer · Direct acting antiviral

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Introduction

In the USA, hepatitis C virus (HCV) infection is a leading cause of liver-related deaths, cirrhosis, and hepatocellular carcinoma [1•, 2•]. HCV was discovered in 1989, but it was not until 1992 that the blood supply was screened for HCV; therefore, prior to 1992, contaminated blood products had been a primary cause of infection [3–5]. Currently, HCV infection is primarily acquired through percutaneous blood exposure, most commonly through injection drug use. In the past, HCV treatments were used infrequently because of side effects and modest efficacy; however, since 2011 and then accelerating since 2013, safe, tolerable, and curative therapies have considerably altered clinical and public health frameworks related to the prevention, control, and clinical management of HCV [3•]. Despite promising advances, significant challenges remain for reducing HCV-associated morbidity and mortality.

Virology, Pathogenesis, and Clinical Course

HCV is an enveloped, positive-sense, single-stranded RNA virus of the *Flavivirdae* family [6–8]. There are 7 major genotypes (6 major genotypes and the recent addition of genotype 7 found in only a few cases) and as many as 100 subtypes identified by lowercase letters [9]. The HCV replication process is error prone, which results in variant viruses known as quasispecies [10, 11]. These virologic characteristics and other host genetic factors can affect an individual's disease progression, ability to clear the virus spontaneously, and response to treatment [3•].

Acute infection with HCV is frequently asymptomatic; however, 25–30% of those acutely infected may have symptoms including fever, jaundice, and abdominal pain [12]. Of adults newly infected with HCV, ~15–25% has spontaneous resolution of their infections [13]. However, the likelihood of resolution varies by age and virologic and host genetic factors [14]. Those who do not resolve their infection develop chronic HCV infection defined as the presence of detectable HCV RNA at least 6 months following the acute infection [13]. Those with chronic HCV infection may develop liver fibrosis of varying severity over time, and ~15–20% of those with chronic infection will develop the most advanced form of fibrosis known as cirrhosis [15]. Rates of liver fibrosis progression are influenced by host genetic factors, age of infection, co-morbid conditions such as diabetes, and certain environmental factors such as concurrent alcohol use, but cirrhosis typically develops over a couple decades [15]. Those with cirrhosis can become decompensated at rates of 2–4% per year or develop hepatocellular carcinoma at rates of 1–7% per year [13]. Additionally, HCV can result in multiple manifestations of extrahepatic diseases including diabetes mellitus, cryoglobulinemia, non-Hodgkin's B cell lymphoma, membranoproliferative glomerulonephritis, lichen planus, and porphyria cutanea tarda [16]. Finally, persons infected with HCV have reported reduced quality of life from symptoms such as fatigue [17].

Modes of Transmission

Bloodborne transmission is the primary mode of HCV transmission [5•]. Unsafe injection practices in healthcare settings and recreational injection drug use are particularly important for HCV transmission worldwide [5•]. Prior to the screening of blood products for HCV beginning in 1992 in the USA, healthcare-associated transmission of HCV occurred more frequently [5•]; however, 33 healthcare outbreaks involving more than 239 outbreak-associated cases were reported to the Centers for Disease Control and Prevention [CDC] from 2008 to 2015 [18]. Vertical transmission can occur in ~6% of infants born to HCV-infected mothers, and transmission may be twice as likely to occur in infants born to HCV/HIV co-infected mothers or HCV mono-infected mothers with high viral loads [19–21]. Sexual transmission is generally inefficient [22]; however, an increasing number of cases of sexually transmitted infection have been reported among HIV-infected men who have sex with men [MSM] [23, 24]. Finally, HCV transmission has also been reported in the setting of non-injection drug use as well as in the setting of unregulated tattoos [25].

Testing and Diagnosis

Laboratory diagnosis of chronic HCV infection in the USA currently requires the use of two types of tests: immunoglobulin (Ig) G antibody enzyme immunoassays (anti-HCV) and nucleic acid tests (NATs) [26•]. HCV testing should be initiated with an anti-HCV antibody test. Persons without risk factors for HCV and a non-reactive anti-HCV antibody require no further evaluation for HCV infection [26•]. Additional testing may be appropriate for certain populations with severely compromised immune systems or current risks for HCV exposure such as injection drug use or hemodialysis [26•]. A reactive anti-HCV antibody requires confirmation with a HCV NAT to determine the presence of HCV RNA and current HCV infection [26•]. Persons with a reactive anti-HCV antibody and a positive HCV NAT are infected with HCV and should be linked to appropriate HCV medical care and treatment [26•]. A person with a reactive anti-HCV antibody and a negative HCV NAT does not have current HCV infection; this may represent (1) spontaneous resolution of a previous infection, (2) sustained virologic response (SVR) following HCV treatment, or (3) a false positive anti-HCV antibody result (although this is rare in populations with risk factors for HCV infection) [26•]. If there is a need to distinguish between true or false positivity of the anti-HCV antibody result, testing may be done with a second FDA-approved HCV antibody assay that is different from the assay used for initial antibody testing [26•].

HCV Testing Recommendations in the USA

HCV testing recommendations in the USA are issued by CDC and the US Preventive Services Task Force (USPSTF) [3–5, 27•]. The American Association for the Study of Liver Disease and Infectious Disease Society of America (AASLD-IDSA) has also issued testing recommendations as part of guidance for HCV care and treatment. Table 1 highlights similarities and differences in the populations currently recommended for HCV testing by each organization. Recommendations are based on the presence of known HCV transmission risk factors as well as estimated prevalence in certain populations [3–5, 27•]. USPSTF and CDC recommend one-time testing with anti-HCV antibody for adults born during 1945–1965 regardless of the presence of known HCV

Table 1 Hepatitis C Screening Recommendations issued by the US Preventive Services Task Force (USPSTF), Centers for Disease Control and Prevention (CDC), and the American Association for the Study of Liver Disease and the Infectious Disease Society of America (AASLD-IDSA)

Risk factor	USPSTF	CDC	AASLD-IDSA
Adults born during 1945–1965	X	X	X
Current or past injection drug use	X	X	X
Receipt of blood transfusion before 1992	X	X	X
Receipt of clotting factor concentrates produced before 1987		X	X
Organ transplant before July 1992		X	X
Long-term hemodialysis	X	X	X
Children born to HCV-positive women	X	X	X
Incarceration	X		X
Intranasal drug use	X	U	X
Other non-injecting illegal drug use		U	
Receipt of an unregulated tattoo	X	U	X
Other percutaneous exposures	X		
Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood		X	X
HIV-infected		X	X
Persistently abnormal alanine aminotransferase (ALT)		X	X
Unexplained chronic liver disease and chronic hepatitis			X
Solid organ donors (deceased and living)			X
Persons with a history of multiple sex partners or sexually transmitted diseases		U	
Long-term steady sex partners of HCV-positive persons		U	
Recipients of transplanted tissue (e.g., corneal, musculoskeletal, skin, ova, sperm)		U	

Adapted from Guidelines and Guidance from US Preventive Services Task Force (USPSTF), Centers for Disease Control and Prevention (CDC), and the American Association for the Study of Liver Disease and the Infectious Disease Society of America (AASLD-IDSA)

HCV hepatitis C virus, *USPSTF* US Preventive Services Task Force, *CDC* Centers for Disease Control and Prevention, *AASLD-IDSA* American Association for the Study of Liver Disease and the Infectious Disease Society of America, *ALT* alanine aminotransferase, *X* HCV testing recommended, *U* Mentioned in guidelines but described as of uncertain need, for HCV testing

risk factors because prevalence is six times higher in that population than among adults born in other years and ~45% of people in this birth cohort report no known exposure risk [see Special Populations and Disparities Section] [3–5, 27•, 28•]. This population has been recommended for testing by CDC since August 2012 and USPTF (Grade B recommendation) since June 2013 [3–5, 27•]. AASLD-IDSA incorporated CDC recommendations into guidance for HCV care and treatment [3–5, 27•]. Finally, all organizations recommend testing for persons of any age with the following HCV-related risk factors: current or past injection drug use, receipt of blood transfusions prior to 1992, receipt of long-term hemodialysis, and children born to HCV-infected mothers [3–5, 27].

Treatment

Historically, the mainstay of HCV therapy had been interferon and ribavirin-based regimens, which were used sparingly because of poorly tolerated side effects and modest efficacy with sustained virologic response (SVR) rates of ~50% [29–31]. In 2011, the introduction of two NS3/4A protease inhibitors used in combination with interferon-based regimens for chronic HCV treatment marked the start of the direct-acting antiviral (DAA) era [29]. Since then, additional drugs comprising interferon-free DAA regimens with cure rates >90% have become available. These drugs target other viral components such as the NS5A protein inhibitors and NS5B polymerase inhibitors. These new DAA regimens are all oral, highly effective, and well tolerated and typically require only 8–12 weeks of therapy for the majority of HCV-infected patients including those with history of previous HCV treatment, decompensated cirrhosis, end-stage renal disease, HIV/HCV co-infection, and recurrent HCV infection post-liver transplantation [32–40]. Additionally, in June 2016, a new treatment regimen effective against all HCV genotypes became available, which has the potential to further simplify HCV treatment protocols [41]. In the USA, treatment is currently recommended for the vast majority of HCV-infected patients, and the latest information on currently available HCV treatment

regimens can be accessed through AASLD-IDSA HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C [3•].

Special Populations and Disparities

There are several populations in the USA that are important to consider because of disparities in HCV prevalence, transmission risk, and clinical management.

Adults Born during 1945–1965

Adults born during 1945–1965, often referred to as "baby boomers," have an estimated anti-HCV antibody prevalence of ~3%, which is six times higher than among other adults [4•, 28•]. Baby boomers are estimated to account for approximately 75–81% of all HCV infections in the USA [4•, 28•]. These differences in prevalence are related to historical factors such as a higher incidence of HCV infections in the 1970s and 1980s and changes in healthcare infection control practices such as injection practices and use of universal precautions [4•, 42–44]. Since most baby boomers were likely infected more than 30 years ago, they are at increased risk of having advanced liver fibrosis (estimated at 27% at time of first diagnosis) and other morbidity and mortality associated with chronic HCV infection [45•]. This has been demonstrated by an average annual increase in the HCV mortality rate of 0.18 deaths per 100,000 population per year during 1999–2007 and an average annual increase in the HCV mortality rate of 0.14 deaths per 100,000 population per year during 2003–2013 [1•, 44]. In addition to rising HCV-associated mortality rates, in the absence of diagnosis and treatment, disease models project rising morbidity rates estimating 1.76 million persons with untreated HCV infection will develop cirrhosis, with a peak prevalence of 1 million cases occurring from the mid-2020s through the mid-2030s [46].

Although the overall prevalence of HCV infection is higher in adults born during 1945–1965 than in adults born in other years, prevalence within this population varies by sex, race/ethnicity, and socioeconomic status. For example, the highest prevalence was found in non-Hispanic black males (8.1 to 13.9%) [4•], and overall, males had twice the prevalence compared with females in the birth cohort [4•]. Additionally, approximately ~30% of adults born during 1945–1965 were found to lack health insurance prior to Medicaid expansion [4•]. In fact, studies evaluating HCV testing of adults born during 1945–1965 in urban emergency departments found HCV antibody positivity rates ranging from 7.3 to 14.7% primarily in socioeconomically disadvantaged populations [47•, 48].

Disparities, which disproportionately affect people of lower socioeconomic status, create challenges for scaling up HCV testing and treatment because of underlying health inequities such as differing healthcare access between groups and health plan and payer-imposed restrictions on HCV treatment to control drug cost expenditures [49–53]. Addressing these disparities is critical, because persons born during 1945–1965 are more likely to have developed or will develop preventable complications of HCV such as decompensated cirrhosis and hepatocellular carcinoma due to many years of chronic HCV infection [46].

People Who Inject Drugs

People who inject drugs (PWIDs) are at increased risk for HCV infection, and the incidence of reported acute HCV infections among young people who inject drugs has been increasing since the early 2000s [18, 54•, 55•]. The incidence of reported acute HCV in young persons observed from 2006 to 2012 was notable for an annual increase in incidence more than two times greater in non-urban compared to urban jurisdictions [54•]. Additionally, reported cases were predominantly of white race, as likely to be female as male, and to have reported previous prescription opioid or powder cocaine use [54•]. Multiple HCV outbreaks among PWIDs in non-urban settings including in Appalachia, southern and western states, upstate New York, Massachusetts, Wisconsin, Virginia, and Indiana have been reported [54–58]. Notably, in 2014–2015, Scott County Indiana was the site of a large HIV outbreak fueled by injection drug use of extended-release oxymorphone; there were 181 outbreak-related HIV infections of whom 167 (92.3%) were co-infected with HCV (58). Furthermore, among the 183 HIV-negative contacts of case patients tested for HCV in Scott County, 116 (63.4%) were HCV positive, which highlights the high HCV prevalence in this population independent of the HIV outbreak [58•].

The sociodemographic characteristics of PWIDs, and stigma associated with injection drug use, create barriers that impede identifying this population and ensuring access to HCV treatment services. Younger PWIDs, particularly those under the age of 30, may not be connected to a "usual source of healthcare," which can create challenges for identifying this population and linking them to care if infected with HCV [59, 60]. Additionally, although current guidelines recommend testing PWIDs for HCV, the stigma associated with this behavior may lead some individuals to deny the behavior and therefore miss an opportunity for testing [61, 62]. Strategies to increase HCV testing and linkage to care in this population have included point-of-care HCV testing at syringe service program sites or other harm reduction sites, co-location of addiction treatment and medical services, community outreach programs, case management, and peer navigators [60, 63•]. Of note, one study at an urban safety net hospital found that PWIDs under 30 years of age were more likely to become

engaged with HCV-related care if they were tested in established outpatient primary care settings compared with testing in inpatient or emergency departments [60]. Finally, one major barrier to treatment access for this population is health plan and payer-imposed restrictions on HCV treatment. Most Medicaid programs have instituted various substance abuse criteria requiring counseling or documented periods of abstinence from drug or alcohol use as a prerequisite for authorizing HCV treatment [64•, 65•]. Although concurrent drug and alcohol use are not contraindications to HCV treatment on the drug label, the health plan and payer restrictions effectively limit access to curative HCV therapy for PWID, a population with ongoing transmission risk behaviors [49, 66, 67].

Reinfection is an important consideration for PWIDs who are still injecting drugs. Data on reinfection rates following HCV treatment in PWIDs are limited but have been reported to range from 1.7 per 100 person-years to 28.8 per 100 person-years [68–72]. Importantly, the risk of reinfection after HCV treatment may vary depending on the local prevalence among PWID populations such that low prevalence settings have lower rates of reinfection [68]. This concept is important because it underpins hypothetical HCV treatment as prevention strategies in models used to reduce the HCV burden and transmission risk in PWIDs [73–75]. Theoretical dynamic models have shown that scaling up DAA treatment to PWIDs in combination with other interventions such as network-based treatment strategies of treating injection partners or combining DAA regimens with opioid substitution therapy and high coverage needle and syringe programs could significantly reduce HCV prevalence and transmission risk [73–75]. For example, one transmission model determined that if opioid substitution therapy and high coverage needle and syringe programs covered 40% of PWIDs, then annually treating 42 per 1000 PWID over 10 years would halve the prevalence for a population with a 60% baseline chronic HCV infection prevalence [73]. These models provide useful insight into the efficacy of scaling up HCV treatment in PWIDs in combination with other harm reduction services; however, additional empirical evidence is needed to validate an HCV treatment as prevention strategy [74].

HIV-Infected MSM

Although sexual transmission of HCV is generally inefficient [22], outbreaks of HCV related to sexual transmission have been reported in HIV-infected MSM in Europe, Australia, Asia, and the USA [23, 24, 76–78]. Factors associated with incident HCV infection among HIV-infected MSM primarily include unprotected receptive anal intercourse with multiple partners, antecedent syphilis, gonorrhea or chlamydial infection, history of injection drug use, having sex with concurrent methamphetamine use, and douching prior to anal intercourse [24, 79•, 80]. In the USA, two studies with national sampling estimated an HCV incidence rate of 0.21–0.51 per 100 person-years among HIV-infected MSM [79•, 81]. These incidence rates, however, may underestimate the true extent of transmission in this population. For example, using mandatory HIV and HCV laboratory reporting data from 2000 to 2010, one study in New York City identified 2016 incident cases of HCV among 41,303 HIV-infected MSM without a history of injection drug [82]. Hispanics and non-Hispanic blacks had higher HCV diagnosis rates than non-Hispanic whites (rate ratio (RR), 1.4 and 1.6, respectively), and MSM diagnosed with syphilis had higher HCV diagnosis rates than those without syphilis (RR 2.5) [82]. These findings suggest a high risk of sexual transmission of HCV in HIV-infected MSM and underscore the importance of testing HIV-infected MSM with ongoing risk factors for HCV at least annually to ensure early linkage to HCV care and treatment services [3•].

Similar to PWIDs, reinfection with HCV after curative therapy or spontaneous resolution is a concern for this population. Studies evaluating HCV reinfection in HIV-infected MSM following HCV treatment and SVR have found reinfection rates ranging from 7.3 to 15.2 per 100 person-years and 2-year cumulative rates of reinfection ranging from 25 to 33% [83–85]. This high reinfection risk highlights the limitations of applying a treatment as prevention strategy for HCV in this population without concurrently addressing ongoing sexual or drug use risk behaviors.

Infants and Children

Annually, an estimated 40,000 children are born to HCV-infected mothers resulting in up to 4000 new perinatally infected children [44, 86, 87]. HCV infection in infants and children is often asymptomatic, but pediatric HCV infection can affect overall health status and cognitive and behavioral functioning; may result in cirrhosis, hepatocellular carcinoma, or liver failure; and results in a 26-fold increased risk of liver-related death [88–92]. Despite the risk of worse health outcomes following vertical transmission of HCV, ~25–40% of infants infected perinatally resolve their infections spontaneously by 24 months, and spontaneous resolution has occurred as late as 7 years after perinatal infection [14]. Approximately 6–12% of infected older children spontaneously resolve their HCV infections, but some studies report rates of spontaneous resolution of ~30% [14, 93]. Infants born to HCV-positive mothers should be tested for HCV [3•, 5•, 27•]; however, diagnosing HCV infection in infants differs from adults because of the presence of maternal anti-HCV IgG, which affects the reliability of anti-HCV antibody results in the first 18 months of life [14]. Therefore, testing for anti-HCV antibody should only be performed in children older than

18 months of age; those with a reactive anti-HCV antibody test should then have a serum RNA test to diagnose chronic infection [14]. Testing for HCV RNA can occur prior to 18 months of age; however, it should not be performed before 2 months of age due to decreased sensitivity of HCV RNA PCR tests in the first few weeks of life [14, 94]. Additionally, HCV RNA detected early in infancy should be rechecked after 12 months to diagnose chronic infection [14]. These diagnostic challenges necessitate close follow-up to ensure that HCV infection status is determined accurately and appropriate linkage to care can be established.

In recent years, there have been increases in HCV detection among women of childbearing age in the USA, which suggest increased risk for mother-to-child transmission of HCV [95•, 96•]. This finding is largely attributable to increases in injection drug use in the USA; for example, from 2011 to 2014, of the pregnant women with anti-HCV positivity reported to the Kentucky Department of Health, 38% reported past or current injection drug use [95•]. This increased risk for HCV infection among young women and, in turn, for mother-to-child transmission of HCV is particularly important because of the limited HCV treatment options for infants and children. The recommended FDA-approved regimen for children age 3–17 years is PEGylated-interferon-[alpha] with ribavirin, which is associated with potential adverse side effects [14]. DAAs are not currently approved for use in infants, children younger than 12 years, or pregnant women because of lack of evidence evaluating safety and efficacy in these populations [3•, 97]. Thus, avoiding adverse outcomes due to vertical transmission of HCV necessitates preventing maternal infection or treating HCV-infected women of childbearing age before pregnancy.

Although children born to HCV-infected mothers should be tested for HCV, there are no recommendations to test pregnant women for HCV unless there is a known HCV risk factor [3•, 5•, 27•]. Despite the recommendations for testing these children, a study linking surveillance and birth certificate data found that in a major US city, 84% of children born to HCV-positive mothers were not adequately tested for HCV infection [96•]. Similar findings of inadequate case ascertainment of children with HCV infection have also been reported in Florida and the USA as a whole [98]. Changes in HCV reporting requirements may help to improve identification of HCV-infected infants [95•]; however, identifying and testing at-risk mothers is the first necessary step for assessing possible risk of vertical transmission and ensuring follow-up of infected newborns. In the absence of a universal testing recommendation for pregnant women, it is essential that HCV risk factors be ascertained in prenatal care. Improved communication between primary care providers, obstetricians, pediatricians, and patients could improve awareness of risk factors and test results to ensure continuity of care for both mother and infant and address substance abuse issues [14, 96•, 99]. Finally, providing HCV treatment to HCV-infected mothers, especially in the postpartum period, could prevent HCV transmission from mother to child in subsequent pregnancies [99].

Continued Challenges

Improving Testing, Linkage to Care, and Treatment Access

HCV prevention efforts are important at multiple points of clinical care as patients proceed from diagnosis to cure (care cascade). An HCV care cascade can serve as a model for identifying opportunities and barriers to improving testing, linkage to care, and treatment access [100•, 101•]. This model can also be beneficial because it can be used to evaluate the effectiveness of interventions used to improve progression along the cascade.

Testing for HCV is the first and most important step in the care cascade. Despite expansion of populations eligible for testing and increased harmonization of testing recommendations [3–5, 27•], an estimated 50% of those with chronic HCV infection have not been tested and are unaware of their infection [28•, 100•, 102]. Successful interventions to improve receipt of HCV antibody and RNA confirmatory testing have included prompts in electronic medical records for identifying eligible patients, immediate phlebotomy and expedited HCV RNA testing for anti-HCV antibody-positive patients, and use of laboratory services that perform reflex testing on anti-HCV antibody-positive specimens [102–106]. A combination of these interventions can be particularly effective. For example, settings with interventions such as reflex RNA testing have increased confirmatory RNA testing among persons with positive anti-HCV antibody results to >85% [102, 106].

The next step in the cascade is linking HCV-infected persons to a healthcare provider capable of providing HCV-specific care and treatment. This can represent a significant barrier on the care cascade. A study of 104 healthcare sites in 21 US municipalities from 2012 to 2014 found that only 41.4% of anti-HCV antibody-positive baby boomers were referred to care and that 32.3% attended the first appointment [107]. In addition to "drop off" associated with failure to attend a primary care provider (PCP) appointment, referral to specialists is another area where patients may fail to progress along the care cascade [102]. Interventions such as case management programs and patient navigators have been shown to be particularly effective for retaining vulnerable patients in care [63, 102]. Additionally, in the era of DAAs and pangenotypic regimens, there are increasing opportunities for PCPs to provide HCV-specific care and treatment. Video conferencing to train PCPs in the management of HCV-infected persons has been used to successfully scale up HCV

treatment in underserved settings [108]. Similar success has been found in non-academic, non-specialist, community health centers in which a training program led by experienced non-specialist PCPs resulted in an increase in the number of PCPs successfully providing HCV treatment to patients with reported SVR rates of 96% [109].

HCV treatment access is the final critical step for completion of the care cascade. Although HCV treatment regimens are well tolerated, of short duration, and highly efficacious, the high cost of treatment and preauthorization requirements from third-party payers represent significant barriers to treatment access [49, 64, 65, 110]. Although treatment of HCV-infected persons is cost-effective from a societal perspective at the initial list price of $83,000–$153,000 per treatment course [110, 111•], even as prices continue to decrease, the cost of HCV treatments can create budgetary issues for payers such as Medicaid programs on 1–2 year budget cycles [110, 112]. For example, in 2014, as much as 6.7% of state Medicaid prescription drug spending was attributable to HCV treatment [96•]. Although guidelines for HCV treatment, allowing PCPs to treat HCV, utilization of services such as patient navigators and case management can improve HCV treatment access [3•, 102, 108], addressing drug pricing and payer restrictions to increase treatment access broadly requires health system level intervention [49].

Vaccination

Despite advances in HCV treatments, the development of an effective HCV vaccine has proven elusive [113, 114]. Vaccine development for HCV has been challenging because of viral characteristics including high sequence variability within protein coding regions, active evasion of the immune system, and evolution of quasispecies from error-prone replication [10, 11, 115]. HCV encodes two surface-exposed glycoproteins, E1 and E2 which mediate viral entry [116]. E2 in particular has been a target eliciting a neutralizing antibody response; however, HCV's immune evasion strategies have limited the effectiveness of this target [116]. Other HCV envelope vaccine candidates tested in humans include those targeting the E1 protein, core-E1E2 DNA, and E1E2 protein [114, 117–120]. A primary T cell-based vaccine candidate has also been tested but failed to induce sufficient response in chronically infected patients in a therapeutic vaccination trial [121]. Despite the lack of a candidate vaccine, modeling strategies have found that even a low efficacy HCV vaccine could halve HCV prevalence and incidence among PWIDs assuming coverage levels comparable to that of HBV vaccine (model based on 72% HBV vaccine coverage among PWIDs in the UK in 2013) [122]. Additionally, DAAs do not offer protective immunity, which may limit the use of DAA therapy as a treatment as prevention strategy [110•]. If DAAs and an effective vaccine could be used concurrently for treatment and prevention, reinfection risk would be expected to drop significantly as the number of individuals susceptible to HCV infection decreases [110•]. However, until a vaccine is developed, prevention strategies aimed at averting incident cases is essential.

Elimination

In April 2016, the National Academy of Sciences released a Phase One report on Eliminating the Public Health Problem of Hepatitis B and C in the USA [123•]. Based on the analysis, the committee concluded that control of HCV is feasible in the relatively short term and that while eliminating HCV is feasible, it will require time and considerable public will, attention, and resources [123•]. Achieving HCV elimination will require sustained efforts and overcoming multiple barriers such as improving public health surveillance, increasing the number of persons who are aware of their infection and linked to care, and improving access to treatment [123•]. The Cherokee Nation of Eastern Oklahoma is the first community in the USA to develop an HCV elimination program [124]. The lessons learned from this program will be critical for identifying effective strategies and methods for reducing prevalence and incidence in communities throughout the USA.

Conclusion

The high burden of HCV and significant health consequences associated with chronic infection make HCV a critical public health priority. Advances in HCV treatment have created new opportunities for reducing HCV-associated morbidity and mortality. These treatments are safe, well tolerated, and highly effective; however, the benefits cannot be realized without a significant increase in the number of persons tested for HCV so that all chronically infected individuals can be aware of their diagnosis and linked to appropriate clinical care. Prevention and outreach efforts to focus on baby boomers and PWIDs in particular will be critical to decreasing prevalence, reducing incidence, and achieving HCV elimination.

Compliance with Ethical Standards

Conflict of Interest Alexander J. Millman, Noele P. Nelson, and Claudia Vellozzi each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Disclaimer The findings and conclusions in this report are those of the authors and do not necessarily reflect the official position of the Centers for Disease Control and Prevention.

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