

Ending hepatitis C in the United States: the role of screening

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Abstract: The US faces at least two distinct epidemics of hepatitis C virus infection (HCV), and due largely to revised screening recommendations and novel therapeutic agents, corresponding opportunities. As only 49%–75% of HCV-infected persons in the US are aware of their infection, any chance of addressing HCV in the US is dependent upon screening to identify undiagnosed infections. Most HCV in the US consists of longstanding infections among persons born during 1945–1965 who are suffering escalating rates of liver-related morbidity and mortality. Mathematical modeling supports aggressive action to reach and treat these persons to minimize the subsequent burden of advanced liver disease on patients and the health care system. Incident infection is primarily among persons who inject drugs, less than 10% of whom have been treated for HCV. Expanded screening and treatment of active persons who inject drugs raises the prospect of utilizing “treatment as prevention” to stem the tide of incident HCV infections in this population. HIV-positive men who have sex with men (MSM) represent a population at risk for sexually transmitted HCV who may also benefit from adjusted screening guidelines to identify both acute and chronic infections. Prisoners also represent a critical population for aggressive screening and treatment. Finally, the two-stage testing algorithm for HCV diagnosis is problematic and difficult for patients and providers to navigate. While emerging therapeutics raise the prospect of reducing HCV-related morbidity and mortality, as well as eliminating new infections, major barriers remain with regard to identifying infections, improving access to treatment, and ensuring payer coverage of costly new therapeutic regimens.

Keywords: HCV screening, HCV treatment, treatment as prevention

Introduction

The US faces at least two distinct epidemics of hepatitis C virus infection (HCV), and due largely to novel therapeutic agents, corresponding opportunities. Established HCV infections are dominated by “baby boomers” born from the mid-1940s to the mid-1960s, the vast majority of whom are at low risk of ongoing transmission, but given the length of time they have been infected, high risk of the sequelae of advancing liver disease.¹ New infections in the US are almost the exclusive provenance of persons who inject drugs (PWIDs), and those who continue to inject risk secondary transmission of HCV.² Additionally, there is increasing evidence that HIV-positive men who have sex with men (MSM) represent an initial group at risk of apparent sexual transmission of HCV.³ If we dramatically improve screening and utilize novel therapeutics with simplified regimens, low toxicity, and high cure rates, we have the opportunity to reduce the morbidity and mortality of established infections and reduce incidence by treating those at risk of secondary transmission.

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HCV has historically received little attention among public health authorities in the US largely due to limited funding. Viral hepatitis receives less than 3% of the funding HIV receives from the Centers for Disease Control and Prevention (CDC).¹ Some recent changes, including the Patient Protection and Affordable Care Act (ACA) and new screening recommendations from the CDC and the US Preventive Health Services Task Force (USPSTF),^{4,5} provide a real opportunity to improve both screening and treatment of HCV. The ACA may increase the number of insured people in the US by as much as 30 million,⁴ with a principal focus on those with lower incomes and youth, two groups at elevated risk of HCV.^{6,7} Moreover, the ACA requires all insurers to cover preventative services given a grade of A or B by the USPSTF, which includes the new CDC HCV screening guidelines. Regarding screening, we have known for some time that behavioral risk factor-based screening was missing the majority (49%–75%) of HCV infections in the US.^{1,8} The reasons for this failure are speculative, but likely include at least some factors particular to US health care, such as legal, economic, and social stigma related to selected risk behaviors (eg, obtaining life insurance may be extremely difficult for any patient who admits to a history of illicit substance use, and until the ACA, many insurers would not cover patients with preexisting conditions). The new approach includes the risk factor-based guidelines as well as screening all persons born from 1945–1965, a population believed to include 75% of all HCV infections in the US. While this change only directly affects what we will refer to as “established infections”, the attention to HCV screening may improve adherence to traditional screening guidelines as applied to PWIDs and other risk groups. Improved screenings of PWIDs in the US is particularly important as the nation is experiencing a dramatic increase in heroin use subsequent to an epidemic of opioid analgesic dependence.^{9,10}

Reducing morbidity and mortality

Three-quarters of the 3–4 million persons in the US infected with HCV were born from 1945–1965.¹¹ Several distinct HCV models, including one by the first author, suggest that this population of HCV-infected persons is resulting in a formidable burden of liver-related cirrhosis, cancer, and death that will peak by 2030 and then finally begin to decline due to mortality (Figure 1).^{12–14} The US is already witnessing the impact of this epidemic. Estimates of annual HCV-related deaths are as high as 80,000,¹⁵ well in excess of any model predictions, suggesting that the true extent of

the epidemic will be well beyond the predictions of these conservative models.

A notable finding from these models is that improvements in HCV treatment will fail to substantially affect this epidemic of end-stage liver disease without substantial improvements in screening to detect those aging persons prior to the development of hepatic cirrhosis. Screening of the population born from 1945–1965, even limited to treatment with pegylated-interferon and ribavirin, has been estimated to reduce the cumulative total of HCV-related deaths from 591,000 to 509,000 deaths (a reduction of 82,000, or 14%) when compared to risk factor-based screening.¹² Based on a model developed by the lead author of this paper, therapies providing a sustained viral response (SVR) rate of 80% would prevent upwards of 7% of HCV-related deaths, an estimate that doubles with broadened screening efforts (Figure 1).¹⁴ In a variation on this model, if 80% of those found to have HCV were referred to specialty care, 80% attended, 80% were treated, and 80% achieved SVR, cumulative HCV-related mortality would be reduced by 12.4%; the addition of screening of 60% of the general US adult population would result in a 19.1% reduction in mortality (Figure 1). These results strongly suggest that broadened screening, such as that recently approved by major US health care bodies, is necessary to actualize the expected public health benefits of improved HCV therapeutics. Even in the context of cure rates approaching 100%, as we anticipate with regimens in the immediate future,¹⁶ the public health benefits remain dependent on finding those with undiagnosed HCV.

Another way to conceptualize care for this population is through the perspective of the HIV care continuum. The HIV care continuum, also referred to as the cascade of care, has been used by the Institute of Medicine and others to gauge the quality of HIV prevention and care provided at local, regional, and national levels.^{17,18} The results suggest several points of intervention to improve the rate of viral suppression in a community and maximize the potential to use “treatment as prevention” (TasP). Most persons with established HCV infection in the US are no longer at high-risk of transmitting HCV to others (the median duration of injecting drugs in the US is 10–15 years and most HCV-infected persons require substantially longer to progress to significant liver disease);¹⁹ thus, TasP does not apply to the majority of HCV-infected persons in the US. However, the cascade can also serve as a guide to the utilization of HCV screening and care services. Figure 2 illustrates one such cascade, including measures that could be readily implemented in an integrated health system (due to insufficient funding and limited reporting

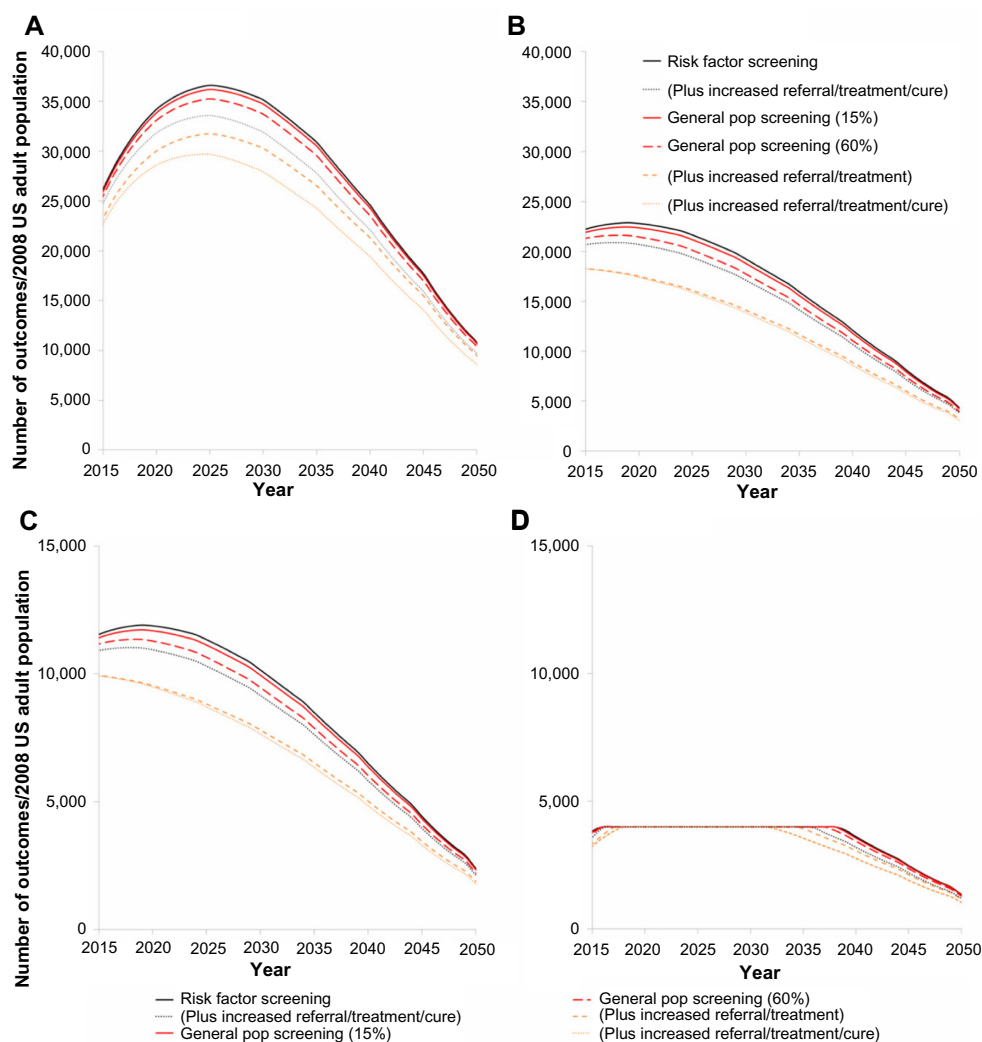


Figure 1 Impact of improved screening, referral, and treatment of hepatitis C on related morbidity.

Notes: (A) Liver-related deaths; (B) decompensated cirrhosis; (C) hepatocellular carcinoma; (D) liver transplants. End-stage liver disease outcomes under: 1) risk factor-based screening plus (1a) improved referral, treatment, and cure rates; 2) addition of screening of 15% of the general population; or 3) addition of screening 60% of the general population plus (3a) improved referral and treatment rates and (3b) improved cure rates, assuming intervention was initiated in 2011. Coffin PO, Scott JD, Golden MR, Sullivan SD. Cost-effectiveness and population outcomes of general population screening for hepatitis C, *Clin Infect Dis*, 2012;54(9):1259–1271, by permission of Oxford University Press.¹⁴

Abbreviation: pop, population.

requirements under various state laws, public health surveillance for viral hepatitis does not currently possess the capacity to track much HCV data, including any negative test results). Data from a large health care provider, Kaiser Permanente (Oakland, CA, USA), have been used to illustrate the screening portion of this cascade, suggesting increased screening in recent years,²⁰ but have not yet been applied to the full continuum of HCV care. The proportion that could be cured by HCV treatment in such a model is limited only by the proportion that would be considered eligible for treatment and by the SVR of dominant therapies.

Historical estimates suggest that less than 2% of persons with HCV are cured through treatment (based on estimates that 25% of persons with HCV are detected through

screening,⁸ 77% are referred to HCV care, 66% attend care,²¹ 26% initiate care,^{22,23} and around 60% achieve SVR). A more recent analysis suggested that as many as 9% of persons with HCV may achieve SVR.²⁴ In contrast, the HCV cascade suggests that, in the setting of therapeutics available in 2013, optimal screening and clinical management could result in cure in up to 30% of persons with chronic HCV. Novel therapies are expected to vastly change these estimates. The absence of interferon and/or ribavirin from regimens will allow many of the 13% with absolute contraindications to those therapies,²⁵ and an additional 50% with relative contraindications,^{22,23,26} to seriously consider treatment, while easier regimens are expected to vastly increase the number of patients willing to engage in treatment. In the setting of

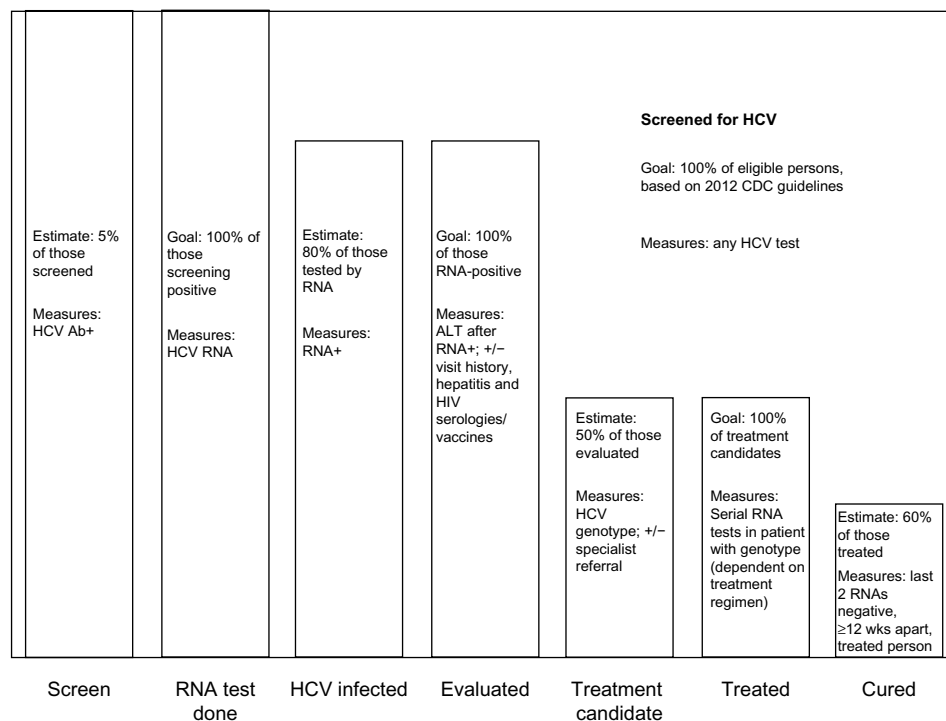


Figure 2 Hepatitis C screening and treatment cascade.

Abbreviations: Ab, antibody; ALT, alanine aminotransferase; CDC, United States Centers for Disease Control and Prevention; HCV, hepatitis C virus; HIV, human immunodeficiency virus; RNA, ribonucleic acid; wks, weeks.

improved SVR, these changes may increase the percentage that could be cured through comprehensive HCV screening and care to as high as 40%–80%. As in the case of HIV, the population-level impact of maximizing HCV outcomes along the cascade is expected to have significant impact on HCV-associated morbidity and mortality, potentially lower transmission, and reduce long-term health care costs. In contrast to HIV, HCV treatment is believed to be curative, which suggests the possibility of more significant socioeconomic and epidemic benefits of improved screening and treatment in the long run.

The advent of novel therapeutics is critical to our efforts to minimize this epidemic of liver disease. High cure rates with more tolerable regimens will not only reduce sequelae among those treated for HCV, but are also expected to entice more HCV-infected persons to seek and accept treatment, thus addressing at least part of the linkage to care gap. Furthermore, the relative simplicity of managing interferon-free therapies will allow a wider range of providers to manage and treat HCV (there are no restrictions in the US on which medical providers can treat patients for HCV, but treatment historically has been offered largely by hepatologists and gastroenterologists because of the complexities involved in managing interferon-based therapies and the historical goal of deferring treatment to await novel therapeutic agents by

performing staging liver biopsies). Two new HCV antivirals, sofosbuvir and simeprevir, were approved for use in the US in 2013 and additional agents are expected to be approved in 2014,²⁷ providing short-course, interferon-free, low side effect, potent options for most HCV-infected persons. Many of the anticipated regimens have similar, high efficacy in populations that respond poorly to interferon-based therapy (eg, those with hepatic cirrhosis or coinfection with HIV), thus expanding the population likely to benefit from treatment beyond that estimated in extant mathematical models. However, the benefits of these dramatic shifts cannot be fully realized without identifying those unaware of their infection through a dramatic expansion in HCV screening.

TasP

In contrast to the vast population of older adults with established HCV infection and low risk of transmission, PWIDs who are actively injecting drugs remain at high risk for both acquisition and transmission of HCV. The CDC estimates close to 18,000 new HCV infections per year, almost exclusively among PWIDs, with a 44% increase in the number of acute cases from 2010 to 2011.²⁸ Several outbreaks of HCV infection among groups of PWIDs have also been noted in recent years, due in part to the vast expansion in opioid prescribing and subsequent transition to injection drug use that

has occurred in communities across the US.²⁹ PWIDs who initiated drug use with prescription opioids are less likely than long-time heroin users to perceive themselves as at-risk for blood-borne viral infections, and thus represent a large cohort of potential infections.³⁰

Syringe exchange has served as the bulwark against HIV infection for PWIDs worldwide. This intervention has been so effective for HIV prevention among this population that most HIV infections among PWIDs in localities with high-quality syringe access may be due to sexual rather than parenteral transmission.³¹ Unfortunately, syringe exchange has not proven nearly as effective for preventing the transmission of HCV. The most optimistic findings suggest that decades of high-volume syringe services have delayed HCV infection such that most PWIDs do not become infected until they have been injecting drugs for about 2 years; given that most PWIDs inject for at least 10 years, syringe exchange does not prevent eventual infection.^{32,33} The suspected reasons for the relative failure of syringe exchange in preventing HCV include the high viral load and high prevalence of infection in the community, as well as the hardness of the virion outside of the body. HCV can survive up to 7 days at 37°C and up to 6 weeks at 40°C and 22°C after drying on inanimate surfaces³⁴ and is found in substantial quantities on all injection equipment, such as cookers, cotton, alcohol pads, and rinse water.^{35,36} These factors likely make HCV much more easy to transmit through practices such as “backloading”, in which PWIDs divide drugs by filling one syringe, pulling out the plunger, and drawing up pre-established amounts of the drug into each personal syringe.³⁷ To prevent HCV through syringe exchange services likely requires not only many decades of ready availability of sterile syringes, needles, alcohol pads, water, cotton swabs, and cookers, but also aggressive educational campaigns to avoid any potential contamination of these materials with other people’s supplies. As evidenced by the ongoing iatrogenic transmission of HCV even in well-regulated health care settings,^{38–40} this may simply be too high of a bar for lay users of injection equipment.

Aggressive screening and treatment, however, have great potential in reducing or eliminating HCV transmission among PWIDs. Recent data suggests that screening positive for HCV results in sustained reductions in drug use among PWIDs,⁴¹ in conjunction with data supporting HCV-based serosorting among PWIDs, these data suggest that screening alone may be helpful in reducing secondary transmission.⁴² Moreover, treatment of active PWIDs for HCV with pegylated-interferon and ribavirin has been found to be cost-effective based on mathematical modeling.⁴³ Experience with treating active

PWIDs in the US, however, suggests that very few would opt for, be eligible for, and successfully complete interferon-based therapy.^{44,45} There are also ethical concerns with treating a high number of active PWIDs with interferon, as most active PWIDs do not yet have advanced liver disease (as the median duration of injecting is 10–15 years);¹⁹ some may never develop liver disease, and there are risks to interferon therapy beyond the relatively transient side effects (eg, permanent hypothyroidism). A more recent modeling exercise examined the use of novel therapeutics for treating active PWIDs. Treating 8%–15% of HCV-infected active PWIDs annually for HCV would reduce HCV prevalence by 75% over 15 years according to a conservative model that assumed that reinfection rates post-treatment were the same as initial infection rates.⁴⁶ Cohort studies, however, estimate the reinfection rate at 4%–6% per year,^{2,47} which is about half the rate assumed for initial infection,⁴⁸ and those trained in safer injection practices may have even less risk of reinfection. Interferon-free therapies may, if widely available, prove viable for mass treatment of active PWIDs.

If we apply the HCV cascade to active PWIDs, the rate of diagnosis remains poor, linkage to care is abysmal, and very few are treated. Although half to two-thirds of PWIDs are HCV seropositive, at least 49% are aware of their diagnosis,¹ around 21% have been evaluated by a provider proficient in treating HCV,⁴⁹ and only 1%–9% have ever initiated HCV treatment. Interferon-free therapies are relatively short, easily dosed, well-tolerated, and highly effective. These improvements should lead not only to high cure rates, but substantially higher rates of treatment uptake. Moreover, the simplicity of managing the regimen should lead to a rapid expansion of HCV treatment into the networks of primary care providers caring for underserved populations such as PWIDs, homeless persons, and correctional populations. If we also take advantage of social networks, and enlist PWIDs within a patient’s network to get screened and treated, we may further reduce the rate of reinfection. If widely employed, these new therapeutics could signal the end of HCV transmission in the US.

Additional areas of concern

HIV-positive MSM

HIV-positive MSM appear to be at risk for sexual transmission of HCV.^{50–53} Although this is a population that is generally under regular medical care and for whom guidelines, including those related to HCV screening, are regularly updated, some studies have found that as many as 30% of HIV-infected patients were unaware of their status.⁵⁴ All HCV-positive

persons should receive an initial screen for HCV, yet that is not always achieved and it remains unclear how frequently HIV-positive MSM should be screened or if repeat testing should only occur based on clinical suspicion (eg, an elevation in transaminases). Recently released HCV management guidelines from the American Association for the Study of Liver Diseases and the Infectious Disease Society of America recommend annual HCV screening for PWID and HIV-infected MSM.⁵⁵ The European AIDS Treatment Network recommends HCV antibody screening for all newly diagnosed HIV-positive persons, annual HCV antibody testing and twice annual alanine aminotransferase testing for MSM at risk for acute HCV, HCV antibody testing 3 months after diagnosis of a sexually transmitted disease or injection drug use exposure, and HCV RNA testing on suspicion of acute HCV.⁵⁶ The development of updated HCV recommendations for HIV-infected persons is particularly relevant as coinfection with HIV and HCV can result in rapid progression of liver disease⁵⁴ and because early detection may provide a superior chance of cure.

Screening in correctional populations

Although HCV seroprevalence among US prisoners is declining, rates still range from 10%–41% and represent 29%–33% of all HCV cases in the country.⁵⁷ Screening guidelines in correctional settings that rely on self-report of injection drug use, a revelation that may raise legal or social difficulties for the incarcerated individual, miss many who should be screened.⁵⁸ In contrast, revised USPSTF guidelines recommend screening all incarcerated persons for HCV, removing the need for self-disclosure.⁵⁹ Routine HCV screening in correctional settings, with access to treatment during incarceration and linkage to care upon release, has the potential to substantially reduce the morbidity, mortality, and transmission of HCV.⁶⁰

Testing algorithm

Knowledge about one's HCV infection is necessary to progress to treatment, and in one study, was the only independent predictor for receiving HCV treatment.⁶¹ Such knowledge also predicts serosorting behaviors among PWIDs.⁴² However, surveillance data demonstrate that only about half of those seropositive for HCV receive confirmatory RNA testing,^{62,63} and even among those receiving appropriate follow-up testing, many do not understand the meaning of the various HCV tests.⁶⁴ For the approximately 20% of persons who are exposed to HCV but spontaneously clear the infection, a positive HCV antibody test without follow-up

RNA testing may result in unnecessary anxiety, diminished quality of life,⁶⁵ and for PWIDs who go on to serosort with HCV-infected persons, increased risk of subsequent reinfection with HCV.⁴² In addition, strategies utilizing HCV RNA testing to identify acute HCV infections in susceptible populations should be further developed and promulgated in guidelines and practice.^{66–68} As RNA assays become less expensive and more easily available, we should reconsider testing algorithms to avoid many of the pitfalls associated with the current two-step process of HCV antibody testing followed by HCV RNA testing.

Primary care management

To care for the increased number of individuals expected to be diagnosed with HCV, primary care providers will need to be able to provide initial management and, ultimately, treatment. Currently, many primary care providers are uncertain what to do following an HCV diagnosis, including what steps should be taken for counseling, screening, and vaccination for syndemic infections, and appropriate management prior to treatment. To address these challenges, professional societies such as the American Association for the Study of Liver Diseases and Infectious Disease Society of America have developed recommendations for the testing, managing, and treating of HCV to guide providers who have not specialized in HCV treatment.⁵⁵ Telemedicine has also proven to be an effective tool to support non-specialists in community health care and correctional settings in managing and treating HCV.⁶⁹ Finally, the CDC and other federal agencies are attempting to increase the capacity of primary care providers to manage HCV, through both grants programs and technical assistance, a process that should alleviate some of the constraints on HCV screening and management.⁷⁰

Costs of HCV treatment

The most substantial barrier to recognizing the benefits of enhanced screening and new therapeutics is likely to be the high cost of novel therapeutic agents. New medications are expected to cost in excess of US\$100,000 for a course of treatment,⁷¹ making them out of reach for uninsured populations and an enormous burden on insurers, particularly the public programs caring for a disproportionate share of HCV-infected persons (in an emergency department-based study of birth cohort screening, 16.7% of publicly insured or uninsured patients were HCV-positive compared with 5.3% of privately insured patients⁷²). It remains unclear how health care payers will cover the new medications. They may, for example, require evidence of advanced fibrosis in

order to pay for treatment or require trials of an interferon-based regimen prior to permitting use of interferon-free therapies. Such decisions would have several unfortunate effects: eg, requiring biopsies would largely restrict HCV treatment to specialists; if patients were required to undergo biopsies, substantially fewer would accept therapy; if advanced fibrosis was required, very few active PWIDs would be treated, and thus we would lose any TasP benefit. While less invasive diagnostics, such as transient elastography, are increasingly found to reliably predict cirrhosis and liver-related events,⁷³ these imaging modalities are not routinely available in most health care settings and do not discriminate between each stage of fibrosis. Thus, to achieve the aims of reduced morbidity, mortality, and transmission of HCV would require a sophisticated prior authorization protocol that accounted for the limitations of primary care and the potential benefits of broader HCV treatment in several populations.

Conclusion

The US is positioned to address twin epidemics of HCV infection, if the health care system can muster engagement in broad screening and payer support for wide treatment of infected persons. The cost-effectiveness of treating long-time infected persons is well-established and justifies an upfront investment to dramatically reduce long-term costs and related mortality. The advent of brief 6–12 week, all oral, well-tolerated, highly potent HCV regimens offers the opportunity to think beyond disease control and towards eradication of new HCV infections. With improved screening, linkage to care, and treatment we may be able to end HCV infection in the US within a generation.

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Disclosure

The authors report no conflicts of interest in this work.

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