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Best strategies for global HCV eradication

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Abstract

Worldwide eradication of hepatitis C virus (HCV) is possible through a combination of prevention education, universal clinical and targeted community screening, effective linkage to care, and treatment with promising new direct-acting antiviral drug regimens. Universal screening should be offered in all healthcare visits, and parallel community screening efforts should prioritize high-prevalence, high-transmission populations including injection drug users, prison inmates, and those with HIV/HCV co-infection. Increasing awareness of HCV infection through screening, improving treatment uptake and cure rates by providing linkage to care and more effective treatment, and ultimately combining education efforts with vaccination campaigns to prevent transmission and reinfection can slow and eventually stop the “silent epidemic.”

Keywords

prevention; universal screening; testing; direct-acting antiviral; cure; linkage to care

Introduction

Although viral eradication has been a persistent public health challenge, it has successful precedent. By 1979, smallpox had been eradicated globally, and polio is close behind, with only three polio-endemic countries remaining worldwide (1, 2). The common thread between these two successes is a vaccine that reduced transmission and effectively curtailed new infections. Through these eradication campaigns, medical science, technology, and public health have demonstrated the global community’s ability to identify, create, deliver, and maintain solutions to eliminate deadly and debilitating pathogens. The success of these campaigns has also proven that political and social will exist to conduct the coordinated, dogged, multi-level work required to implement such solutions. With the promise of safe, all-oral, direct-acting antiviral treatments that can provide a functional cure for hepatitis C virus (HCV) as early as 2014, the global community can rise to the renewed challenge not only to prevent new cases, but also to seek, test, and treat existing HCV infections to eradicate another global pathogen.

Global HCV Burden

HCV was first identified in 1989 as the principal cause of post-transfusion non-A non-B hepatitis, and an estimated 130–170 million people worldwide (2–3% of the population) are currently infected (3, 4). Prevalence varies by region, ranging from 0.01%–0.1% in parts of the United Kingdom (UK) and Scandinavia to 15–20% in Egypt (5–8). However, true

prevalence is elusive due to the asymptomatic nature of HCV and inadequate surveillance infrastructure in many countries.

Because most infections are asymptomatic, up to 75–90% of HCV-positive individuals in some regions are unaware of their infection (9, 10). As a result, they remain reservoirs for further transmission and frequently progress to advanced fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Approximately 27% of cirrhosis and 25% of HCC cases globally can be attributed to HCV (11). These percentages are even more staggering in high prevalence countries such as Japan, where HCV accounts for up to 88% of reported HCC cases (11).

Over 350,000 deaths have been attributed to HCV infection annually since 2002, most due to cirrhosis and HCC (12). Recent country-specific estimates based on death certificate analyses approximate 3,500 HCV-related deaths in France in 2001, 7,379 in Egypt in 1999, and 15,000 in the US in 2007. In Egypt, HCV-related mortality is expected to increase 2.1-fold by 2020 (13–15). HCV-infected individuals have 2.4 times the risk of all-cause mortality compared to the non-infected population, 26.5 times the risk of liver-related mortality, and 1.8 times the risk of non liver-related mortality (16). In 2007, HCV-related mortality surpassed mortality from HIV in the United States (US), primarily due to end-stage liver disease among members of the 1945–1965 birth cohort who have been living with HCV infection for 20–30 years (14).

Despite increasing morbidity and mortality from HCV, surveillance is incomplete, out of date, and in some countries non-existent, severely hindering treatment efforts. In the United States, local health jurisdictions use inconsistent case definitions to identify infections, and state laws mandating case reporting by physicians, hospitals, and laboratories vary (9, 17). Supplementary sero-surveillance mechanisms like the US Centers for Disease Control and Prevention's (CDC) ongoing National Health and Nutrition Examination Survey (NHANES) exclude marginalized groups such as prisoners and homeless or institutionalized individuals, many of whom have higher rates of risk behaviors and higher HCV prevalence compared to the general population (18). Several EU countries have recently strengthened their surveillance systems, though they face similar challenges in reaching groups at highest risk (10). Globally, the lack of funding for comprehensive, coordinated surveillance systems, coupled with the asymptomatic nature of most HCV infections, results in fragmented reporting systems that underestimate the true burden of disease. Improving surveillance will not only enhance epidemiologic understanding of HCV, but will also identify the highest priority groups for targeted prevention, testing, and treatment toward eradication.

Prevention: Focus on Transmission

To eradicate HCV, transmission opportunities must be eliminated in three ways: screening for HCV and educating those who test positive about how to avoid infecting others, treating those who test positive to remove them from the pool of transmitters, and changing policies and behaviors to prevent both new infections in the uninfected and reinfection among those successfully treated. Strategies to prevent new infections should be tailored to address the most common modes of transmission in each region.

Percutaneous contact with infected blood accounts for most HCV infections worldwide, but primary modes of exposure vary geographically by countries' economic status. With the advent of effective HCV screening in 1992, injection drug use replaced infected blood and tissue donations as the primary source of new infections in developed countries (12, 19). Although injection drug use contributes to transmission in developing countries as well, most infections in resource-poor areas result from healthcare-related exposures, primarily unsafe injections, which are estimated to account for 2 million new infections per year and 40% of global infections, and unscreened blood and tissue donations (12, 20). According to a 2007 World Health Organization blood safety survey, 20% of responding countries did not screen donations for HCV, and many reported reliance on commercial donors, who tend to have higher HCV prevalence compared to volunteers (21).

Sexual transmission of HCV remains controversial, particularly among heterosexual, monogamous partners. Although some studies report sexual transmission confirmed by molecular typing, with likelihood of transmission increasing with relationship duration (22–24), others have found little or no evidence of sexual transmission among partners and emphasize the likelihood of alternate parenteral household exposures including sharing of needles, diabetic lancets, syringes, razors, and toothbrushes (25–29). Based on retrospective cohort studies, sexual transmission of HCV is relatively rare in monogamous heterosexual relationships, ranging from 0–0.6% per year compared to 0.4–1.8% per year among heterosexuals with multiple partners and those at risk for other sexually transmitted infections (29, 30). In addition, exposure to bleeding caused by intimate partner violence has been associated with HCV infection (31). Although sexual transmission appears to be low among these subgroups, as much as a 23-fold increase in HCV transmission among HIV-infected men who have sex with men has been associated with high-risk sexual behaviors (29, 32–34). Vertical transmission is also possible, though rare; an estimated 4–7% of babies born to HCV-positive mothers acquire infection (35, 36).

Prevention efforts should address all modes of transmission, though strategy prioritization will differ depending on the specific transmission patterns in each target community, city, or country. For example, in Egypt and other high-prevalence developing countries, modifying injection practices (emphasizing single-use syringes and intensifying education for healthcare workers) and standardizing blood donation screening will have the greatest impact, while needle exchange programs and education through substance abuse treatment clinics, primary care physicians, and sex and drug education in middle and high schools will likely offer the greatest return in the US and other developed countries.

Egypt provides an example of targeted prevention efforts that produce impressive results in local high-risk populations. Egypt's 15–20% HCV prevalence is the result of mass schistosomiasis treatment campaigns in which improperly sterilized syringes propagated HCV infection (6). Healthcare settings remain one of the primary sources of new infections. However, infection control practices put in place by the Egyptian Ministry of Health in 2001 have resulted in a decrease in annual HCV incidence among dialysis patients from 28% to 6% between 2001 and 2012 (37), demonstrating effective, targeted prevention.

The Changing HCV Treatment Landscape

Past and Current Treatment

In addition to preventing new cases, existing infections must be effectively treated to achieve eradication. The polio and smallpox eradication campaigns utilized vaccines to halt transmission through herd immunity. Although no effective HCV vaccine currently exists, promising new direct-acting antiviral (DAA) treatments can work toward the same goal by eliminating the virus, one host at a time. Once successful vaccines have been developed, local health departments can partner with pharmaceutical companies, clinicians, media organizations, and advocacy groups to implement vaccination campaigns with both prophylactic and therapeutic value.

HCV treatment options have evolved rapidly, progressively improving efficacy and reducing therapy-induced side effects. Cure rates, measured by sustained virologic response (SVR), have increased from just 10% among patients treated with interferon monotherapy in 1990 to 80% in some genotypes with current standard of care (SOC) treatments, and are expected to climb to 90% or more with the adoption of DAA regimens currently under evaluation in clinical trials (38–43).

Current SOC treatment and SVR rates vary by genotype. Pegylated interferon plus ribavirin (peg-IFN/RBV), administered for 24 weeks, achieves SVR in up to 75–80% of non-cirrhotic individuals with genotypes 2, 3, 5, and 6 HCV (43–46); 48 weeks of this treatment regimen yields up to 70% SVR for genotype 4, which accounts for approximately 20% of global infections, primarily in Africa and the Middle East, particularly in Egypt where genotype 4 accounts for 90% of HCV cases (47, 48). In non-cirrhotic genotype 1 infected individuals, who have historically been more difficult to treat, the addition of a protease inhibitor (telaprevir or boceprevir) to 48-week treatment has increased SVR from 40% to 70% (49, 50). SVR has been consistently predicted by viral genotype, IL28B polymorphism, non-black race, absence of cirrhosis, low viral load, and most recently, early treatment (48, 51–53).

Despite increases in treatment efficacy, estimates of uptake are low, ranging from 10% in Canada and 12–25% in the US to 41% and 44% in Belgium and Germany, respectively (54–59). Numerous medical and patient-related factors influence the likelihood of treatment after diagnosis. Perhaps most importantly, the debilitating flu-like symptoms and depression associated with interferon, and anemia caused by ribavirin, contribute to treatment avoidance in eligible patients and adherence problems and discontinuation in many who are treated (58, 60). In addition, an estimated 23% of newly-diagnosed patients in the US and 51% in the UK are not referred to a specialist after diagnosis (61, 62), often because diagnosing physicians advise patients in early fibrosis stages to postpone treatment, hoping that more effective drugs will be developed before treatment is unavoidable (58, 63).

All-Oral, Interferon-Free Treatments

With the introduction of all-oral DAA drug combinations that eliminate interferon and its side effects, treatment uptake is expected to increase. Some of these investigational regimens have achieved SVR in more than 90% of some subgroups in clinical trials,

including null responders to prior interferon-based treatment (Table 1) (38–40, 64, 65). As these regimens become available, physician confidence in treatment outcomes will likely increase, concerns about side effects will gradually subside, and specialist referral may not be necessary for treatment, resulting in higher uptake and more infections cured.

For non-genotype 1 infections, most of these DAA regimens will likely include a nucleoside analog as a backbone, combined with ribavirin. For genotype 1 infections, this nucleoside backbone may be combined with a second nucleoside with a different phosphorylation pathway and/or a protease inhibitor, NS5A inhibitor, non-nucleoside inhibitor, or cyclophilin inhibitor, all with high genetic barriers to resistance, with or without RBV (66). Eventually, even for non-genotype 1 infections, both ribavirin and interferon will likely be eliminated, removing many of the side effects associated with SOC regimens. It is also possible that DAA regimens without a nucleoside analog may be successfully developed, although the pill burden and dosing frequency may increase and they may not be pangenotypic. These new DAA treatments are expected to increase SVR rates by preventing selection of drug resistant viruses and leveraging the lack of latent phase in HCV replication (67). Treatment duration with DAA regimens is expected to be 12 weeks, but as more potent, once-daily “one-size fits all” DAA options become available, treatment could be reduced to 6–8 weeks.

Because all-oral regimens will likely be expensive, access to treatment will continue to be a barrier to eradication. To improve access, response-guided treatment should be considered, in which SOC regimens are supplemented with a DAA for nonresponders. Similar strategies utilizing protease inhibitors for genotype 1 nonresponders have been shown to be cost-effective (68).

Cost-Effectiveness of All-Oral Treatment

In early analysis, a generalized all-oral HCV treatment regimen resulted in lower costs and more quality-adjusted life years (QALY) gained compared to SOC treatment in genotypes 1, 2, and 3. QALY gained per dollar spent were maximized in younger treatment cohorts due to longer life expectancy and slower disease progression, though the degree of cost-effectiveness of these regimens will depend upon the final cost of all-oral drugs, as well as the willingness-to-pay threshold set by interested stakeholders (69).

As the new DAA regimens become available in developed countries, the prices of interferon and first generation protease inhibitors are expected to decrease. Due to the anticipated high cost of patented DAA drugs, especially for developing countries, additional cost-effectiveness analyses are warranted for non-genotype 1 treatments comparing SOC alone (peg-IFN/RBV) *versus* response-guided therapy with SOC plus a DAA.

Vaccine Development

Although there is not yet a successful vaccine against HCV, development efforts for vaccination as both treatment and prophylaxis are ongoing (70–73). Because vaccines may be more effective in individuals with a low viral load, vaccination could be a promising

addition to antiviral therapy, especially among injection drug users (IDU) and other groups at high risk for reinfection (71, 74).

Genetic diversity among the six HCV genotypes has been estimated to be ten-fold higher than that of HIV, making a single vaccine for all genotypes challenging to formulate. Thus, vaccines for individual genotypes, with targeted delivery based on variable geographic genotype prevalence, may be more tenable (74). Ultimately, successful treatment of existing infections, coupled with vaccination to prevent new infections, can stop the cycle of transmission and eradicate HCV.

Test to Treat: Lessons Learned from the Front Lines

Regardless of their clinical efficacy, DAA regimens will be powerless against the virus among the 75–90% of HCV-positive individuals who are unaware of their infection. To shrink the pool of transmitters through treatment, these individuals must first be identified. Universal HCV screening should become the standard of care among primary care clinicians, replacing current risk factor-based screening. In parallel, targeted community-based screening and treatment uptake efforts should be prioritized among high prevalence, high-risk groups where infections are most likely.

Implement Universal Screening

Currently, risk-based screening is considered the most cost-effective HCV screening strategy and is recommended by CDC (35, 75). However, because some infected individuals do not have a history of traditional HCV risk factors (including injection drug use, blood transfusion prior to 1992, and elevated liver enzyme levels), it is estimated that risk-based methods would identify only 85–87% of infections in the US (76). HCV eradication cannot occur if clinicians continue to use a screening strategy that misses 13–15% of infections among those who seek care.

In a survey of individuals seeking outpatient care at a large urban medical center in the US, 85% were in favor of universal HCV screening during clinician visits. Of those in favor, 37% preferred an “opt-out” option (77). With appropriate consent in place, universal opt-out HCV screening could be added to any clinical blood draw, allowing more infections to be identified in early stages before cirrhosis and liver cancer develop. Foregoing screening and postponing treatment will result in more advanced chronic infections with lower likelihood of SVR when ultimately treated, leading to increased costs to hospitals, insurers, and individuals as well as increased morbidity and mortality (78, 79).

In a recent analysis by Singer et al., universal screening was cost-effective if 50% of those diagnosed initiated treatment. Depending on the country, there is a long way to go to reach 50% treatment uptake. The introduction of DAA regimens will undoubtedly contribute, and could even achieve the 50% mark through enhanced clinician confidence, the possibility of treating in primary care, and side effect reduction. However, the true goal is not just cost-effectiveness, but eradication, which will require even higher treatment percentages.

To achieve this goal, universal clinical screening should be coupled with parallel, community-based screening campaigns targeting high-risk, high-prevalence groups, many of which do not seek medical care and would not be reached with clinical screening. These campaigns should focus on an integrated approach including screening, linkage to care, treatment, and community support.

Prioritize High-Risk Groups

In the European Union (EU), efforts to improve HCV awareness and testing have increased treatment rates. For example, an HCV prevention program initiated by French national hospitals in 1999 resulted in a 32% increase in awareness of infection and a 24% decrease in detectable HCV RNA levels among HCV-positive individuals between 1994 and 2006 (80). France now has the highest HCV treatment rate across the EU (10). Similarly, enhanced surveillance and prevention efforts in Scotland since 2006 have doubled the number of HCV-positive individuals treated, including a five-fold increase in treated prisoners (10).

Both of these successful programs targeted screening efforts to populations at high risk of infection including IDU, immigrants from high-prevalence countries, and prison inmates. To make the greatest impact, individual governments should prioritize free screening among these and other high-prevalence groups, and deliver screening and treatment in accessible, non-traditional settings such as drug rehabilitation clinics, domestic violence shelters, and mobile screening units. Mobile medical clinics in urban settings can effectively reach a large number of individuals at high risk for HCV and HIV, including IDU and those participating in commercial sex work (81).

Chief among these high-risk groups are IDU, prison inmates, those with HIV/HCV co-infection, and the 1945–1965 birth cohort. Because of the high prevalence of HCV among these groups, screening will yield a high ratio of identified cases to screenings conducted, providing a unique opportunity for case identification leading to treatment and cure.

Injection Drug Users—IDU account for an estimated 40% of known HCV infections in the EU overall, 60% in the US, and up to 97% in England and Wales (5, 82, 83). Prevalence of HCV infection among IDU ranges from 41% in England and Wales to 65% in the EU overall, and up to 80% in the US and 81% in Denmark (82–84). High prevalence in these populations is coupled with low awareness of infection, contributing to further transmission; only 23–49% of HCV-diagnosed IDU report being aware of their infection (82, 85).

In addition, transmission among IDU is beginning to affect younger age cohorts than previously observed. Despite overall downward trends in reported acute HCV incidence in the US, recent enhanced surveillance efforts have uncovered increasing incidence among 15–24 year-old IDU, highlighting the urgent need for drug education for adolescents and targeted screening for this high-transmission group (86). Partnering with schools, religious institutions, community and popular media groups, substance abuse treatment programs, and needle exchanges to provide screening for this population should be a high priority.

Once identified, infected IDU should be linked to care and offered treatment, in addition to opportunities for community support to encourage adherence. Treatment uptake rates among

IDU are generally low, estimated at 3% and 5% in Australia and Canada, respectively (87). Barriers to HCV treatment among IDU include physicians' concerns about treatment adherence and reinfection due to continued drug use, as well as co-morbid psychiatric conditions (88). However, numerous studies have demonstrated successful HCV treatment in IDU populations (89–91), especially when enrollment in care is ensured before, during, and after a decision to initiate treatment has been made (87). A recent model suggests that treating 40 infections per 1,000 IDU annually over a 10-year period would result in a 72% reduction in that population's HCV prevalence, even allowing for reinfection after treatment (92). Furthermore, IDU who have access to needle exchange programs have shown a reduction in the high-risk needle sharing behaviors that lead to reinfection (93, 94).

Directly-observed HCV treatment programs that are integrated with substance abuse treatment, education, peer support, and linkage to tertiary care have shown the greatest success among IDU (89). For example, a recent cohort study of current and former Canadian IDU diagnosed with HCV reported 51% treatment uptake when subjects were enrolled in peer support groups and directly-observed treatment, which provided a forum for regular follow-up and education (87). Thus, providing HCV treatment to IDU in integrated settings such as methadone maintenance clinics can help them manage their drug addictions and co-morbid conditions, including alcoholism, which has been associated with accelerated disease progression and mortality (15, 95). In addition, integrated approaches can provide greater continuity of care during treatment, leading to better treatment outcomes and reduced HCV prevalence.

Prison Inmates—HCV prevalence in the US corrections system is estimated between 12% and 35%, and those released from prisons and jails could account for up to 29–43% of the HCV-infected population in the US (96). Current federal and state laws recommend HCV screening in prisons based on self-reported risk factors, which are vastly underreported due to fear of self-incrimination and distrust of the prison system (97, 98).

Regulations for HCV screening in correctional settings should follow the footsteps of HIV screening, which is offered universally to all inmates at the time of incarceration (99). Many could then be treated while in prison or referred to care in clinical or community settings when released (96). In a study of prison inmates in the UK, those referred to care after HCV diagnosis demonstrated 100% referral attendance, though referral occurred at a lower rate among inmates compared to the general population (18.4% and 64.3%, respectively) (62). Thus, screening for HCV in prisons would not only identify a large number of infections due to high prevalence, but could also lead to high rates of specialist care and treatment, contributing to overall eradication efforts.

HIV/HCV and HBV/HCV Co-Infection—HCV screening should also leverage the existing infrastructure built for HIV and HBV testing. Partly due to shared modes of transmission, particularly injection drug use, an estimated 25% of HIV-infected individuals and up to 90% of HIV-infected IDU are co-infected with HCV (84, 100). Estimates of HCV co-infection among HBV-infected individuals range from 3% in Thailand to 22% in Japan and 23% in the UK, up to 30% in Spain (101–104).

The increased availability of antiretroviral therapy against HIV in developed countries allows HIV-positive individuals to live longer lives, but those who are co-infected with HCV now have time to develop the long-term complications associated with HCV infection. As a result, liver disease from HCV is the leading non-AIDS cause of death among co-infected individuals in the US (84, 105). Because co-infection has been shown to speed disease progression for both infections, HIV-infected individuals should be high priorities for HCV screening and treatment (84, 100, 106). With appropriate consent in place, adding an HCV test to any blood draw testing for HIV or HBV would be a simple and inexpensive strategy to target these important high-risk, high-transmission populations.

However, bundling HCV and HIV screening will not be enough to reach this group. Like IDU, few HIV/HCV co-infected individuals (approximately 10% in the US) actually receive HCV treatment, and most who do are treated by HIV primary care physicians, many of whom have relatively little experience administering interferon-based regimens (63). Once all-oral treatments are available, the lack of specialists may be less problematic, but until that time, linkage from diagnosis to specialist care will be an important strategy to increase treatment uptake among HIV/HCV co-infected individuals.

Over the past three decades, the social visibility of HIV has brought together diverse communities to organize and advocate for the same issues of funding for screening, surveillance, prevention, and access to care and treatment that HCV now faces (12). A partnership with HIV advocates and clinical stakeholders can improve identification of both diseases and speed HCV eradication among co-infected groups. That momentum and infrastructure can then be leveraged to do the same in the general population.

1945–1965 Birth Cohort—Recent research has demonstrated that two-thirds of HCV-infected individuals in the US belong to the 1945–1965 birth cohort (baby boomers), many of whom were infected before the discovery of HCV and are now reaching late stage liver disease as a result of long-term chronic infection (14, 76). In response to this age-based concentration of disease, as well as analysis demonstrating the cost-effectiveness of birth cohort based HCV screening (79), CDC now recommends one-time universal HCV screening in the US for adults in this age group (107). Enhancing these recommendations with strategies to provide linkage to care and treatment will increase overall treatment uptake and cure. However, although this birth cohort is an important screening target due to its size, it is even more critical to prioritize screening and treatment for populations with high transmission rates, such as IDU.

Children and Pregnant Women—Approximately 4–7% of babies born to HCV-positive mothers acquire infection (35, 36). Although perinatal transmission is rare compared to other modes of transmission like injection drug use, it results in 7,500 infected babies each year in the US, where 0.7% of pregnant women are HCV-positive (36). The impact is even more sobering in countries like Egypt, where HCV prevalence among pregnant women has been estimated at up to 11% (108, 109).

Universal screening of pregnant women is not recommended because it is not considered cost-effective. Instead, most physicians use risk factor and symptom-based screening

methods (36, 110). However, risk-based screening poses the same sensitivity problems among pregnant women as it does in the general population. For example, a cohort study among pregnant women and their infants in Pakistan found that risk of antenatal HCV infection was not associated with maternal self-reported risk factors, evidenced by infants who acquired infection from mothers who did not have a history of HCV risk factors (111).

In addition, HCV-positive women cannot currently be treated with SOC therapy during pregnancy, because ribavirin is teratogenic (36). However, regardless of the ability to treat women during pregnancy or the cost-effectiveness of screening asymptomatic individuals, universal HCV testing should be implemented among pregnant women to identify children who should be monitored for signs of infection after birth, and to provide linkage to specialist care and treatment after delivery.

Because multiple providers are involved in treating an HCV-infected pregnant woman and her child during pregnancy (obstetrician) and after delivery (primary care physician and pediatrician), the risk of loss to follow-up is amplified, and continuity of care is especially important. Obstetricians referring infected mothers to specialist care during pregnancy and encouraging specialist attendance at follow-up visits will help to maximize their likelihood of treatment after delivery and appropriate monitoring for their children.

As safer, non-teratogenic treatments become available with the introduction of DAA regimens, it may be possible to treat HCV-infected mothers in their third trimester to reduce viral load and prevent perinatal HCV transmission. Similar approaches using antiretroviral agents among HIV-infected pregnant women have been shown to successfully reduce perinatal HIV transmission worldwide (112–114).

Overlap Between High-Risk Groups—Many individuals at high risk for HCV infection belong to multiple high-prevalence populations, amplifying their risk of infection. For example, the highest prevalence estimates among homeless individuals have been found in groups that are also HIV-infected (61–64%), and the highest estimate of prevalence among veterans comes from a group that is also homeless (44%) (18). Furthermore, risk of perinatal transmission increases among mothers who use injection drugs during pregnancy (110, 115) and is 2–3 times higher among mothers who are co-infected with HIV (35). This overlap exemplifies the need for coordinated, community-based screening and education campaigns that target multiple, often interconnected populations at high risk for infection.

Conclusions: Curing a Plague

Unlike smallpox and polio, HCV does not often cause visible scars or debilitations that inspire the public to advocate for solutions; it is because chronic HCV infection rages internally with few overt symptoms that it has been called a “silent epidemic” (9). The long latent period of HCV infection not only decreases the likelihood of early diagnosis and treatment, but can also impede the public awareness that is necessary to fully eradicate the disease. However, the silence of HCV’s forward march must be met with resonant opposition.

Awareness is the primary limiting factor for HCV eradication. Universal clinical screening for all age groups, coupled with targeted community screening for high-risk groups including IDU, prison inmates, and those with HIV/HCV co-infection, will markedly reduce the number of “silent” infections worldwide. Once unmasked, these infections will be met with a range of safe and powerful treatments, and eventually a vaccine, that can cure and prevent reinfection toward ultimate eradication. For these treatments to have full effect, however, education, community support, and effective linkage to care and follow-up will be essential to maximize treatment uptake. A summary of recommendations toward HCV eradication is provided in Table 2.

To enact these recommendations, governmental, healthcare, and public responses to HCV must intensify and become proportional to the burden of disease. Education is necessary across age groups and in diverse settings including schools, colleges, community centers, religious institutions, healthcare clinics, drug rehabilitation clinics, needle exchanges, prisons, and hospitals. This education must then translate to advocacy, confronting government officials with the responsibility to prioritize screening and treatment, rather than handing subsequent administrations a burgeoning population of infected individuals progressing toward end-stage liver disease and premature death. Governments must cultivate the political and financial will to step up to the opportunity to eradicate another global plague. With the rapid progress of science and the availability of highly effective DAA treatment regimens, governments have a moral obligation to provide care and a cure for all identified HCV-infected individuals.

Only early detection and access to treatment can reduce global HCV-related sequelae, mortality, medical costs, and losses of productivity and quality of life. However, the ultimate benefit of HCV eradication will be measured not by the costs it avoids, but by the lives it saves.

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Abbreviations

HCV	Hepatitis C virus
UK	United Kingdom
HCC	hepatocellular carcinoma
US	United States of America
CDC	Centers for Disease Control and Prevention
NHANES	National Health and Nutrition Examination Survey
DAA	Direct-acting antivirals
SVR	Sustained virologic response

SOC	Standard of care
peg-IFN	Pegylated interferon
RBV	Ribavirin
QALY	Quality-adjusted life years
IDU	Injection drug users

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Table 1

Selected Clinical Trial Results from All-Oral HCV Drug Regimens (as of October 2012).

Study Arms	Viral Genotype	Treatment Experience	Duration	N	SVR4	SVR12	SVR24	Source
Sofosbuvir + Daclatasvir with Sofosbuvir lead-in	1a/1b	Naïve	24 wks	15				(116)
Sofosbuvir + Daclatasvir				14	100%	100%		
Sofosbuvir + Daclatasvir + RBV				15				
Sofosbuvir + Daclatasvir with Sofosbuvir lead-in	2/3	Naïve	24 wks	16	88%	88%		
Sofosbuvir + Daclatasvir				14	100%	100%		
Sofosbuvir + Daclatasvir + RBV				14	86%	86%		
Sofosbuvir + RBV	1	Naïve	12 wks	25	88%			(64)
				17	59%			
ABT-450 + ABT-333 + ABT-267 + Ritonavir + RBV	1	Naïve	12 wks	79	99%	99%		(117)
		Null/partial responders (pegIFN + RBV)		45	93%	93%		
ABT-450 + ABT-072 + RBV	1a/1b	Naïve	12 wks	11	100%	91%	91%	(38)
ABT-450 + ABT-333 + RBV	1a/1b	Naïve	12 wks	33	94%	94%		(39)
		Null/partial responders (pegIFN + RBV)		17	47%	47%		
Daclatasvir + Asunaprevir	1b	Null responders (pegIFN + RBV)	24 wks	21	91%	91%	91%	(65)
	1b	Treatment Ineligible/ Intolerant (pegIFN + RBV)	24 wks	22	86%	64%	64%	
Daclatasvir + Asunaprevir + BMS-791325	1	Naïve	12 wks	16	94%			(121)
Mericitabine + Ritonavir-boosted Danoprevir + RBV	1a	Naïve	00000024 wks	43		26%		(118, 119)
		Naïve		21		71%		
	1b	Partial responders (pegIFN + RBV)		23	44%			
		Null responders (pegIFN + RBV)		29	72%			
Alisporivir monotherapy	2/3	Naïve	24 wks	18			72%	(120)
Alisporivir + RBV	2/3	Naïve	24 wks	61			92%	(120)
BI 201335 + BI 207127 + RBV	1	Naïve	16 weeks	81	70%	59%		(122)
			28 weeks	78	76%	68%		
			40 weeks	77	56%	39%		

Table 2

Summary of Recommendations Toward HCV Eradication.

Strategy	Recommendations
Infection Identification	<ul style="list-style-type: none"> • In all healthcare visits, replace risk factor-based screening with universal screening for all age groups, including pregnant women • Implement universal screening for prison inmates • Bundle HCV testing with blood draws for HIV and HBV tests • Utilize existing infrastructure to conduct community-based screening campaigns among high-prevalence and high-risk populations that do not traditionally seek clinical care (IDU, immigrants from high-prevalence countries, veterans, HIV/HCV and HBV/HCV co-infected, homeless individuals, and victims of sexual assault and intimate partner violence) • Target those who belong to multiple high-risk groups • Change attitudes to promote empowerment through creative, accessible, artistic advertising highlighting the dangers of HCV and the availability of a cure • Increase the use of mobile medical clinics in urban settings to reach out to the large number of individuals who do not have medical coverage and/or do not access medical care
Treatment	<ul style="list-style-type: none"> • Provide access to a universal minimum standard of care for HCV infection • Effectively link screening and treatment • Identify and mitigate factors that reduce adherence; build capacity for community/peer support to increase chances of success • Once approved, adopt DAA-based regimens, or response-guided SOC+DAA in resource-constrained areas • Reduce transmission by prioritizing DAA treatment in high-transmission populations including IDU • Continue to invest in research to develop safe, potent drugs with a high genetic barrier to resistance • Develop safe treatments for pregnant women to prevent perinatal transmission, and for infected children so they can lead normal lives • Continue therapeutic vaccine development
Prevention	<ul style="list-style-type: none"> • Coordinate education on transmission, risk, and health consequences of HCV among schools, religious institutions, media outlets, health departments, community centers, clinicians, drug rehabilitation centers, and other stakeholders • Combine creative outreach campaigns (see above) with education about transmission risks and health consequences of HCV • Continue prophylactic vaccine development • Collaborate with community programs to prevent and reduce intimate partner violence and sexual assault, which could become important HCV risk factors
Advocacy	<ul style="list-style-type: none"> • Leverage education efforts to promote grassroots advocacy for public and private funding for improved surveillance and access to screening and care • Partner with HIV advocates and clinicians to increase visibility and benefit from best practices • Focus on ever-rising costs of care in the growing population of untreated infected individuals