Liver INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF THE LIVER

Liver International ISSN 1478-3223

REVIEW ARTICLE

Best strategies for global HCV eradication

Liesl M. Hagan and Raymond F. Schinazi

Center for AIDS Research, Emory University School of Medicine and Veterans Affairs Medical Center, Decatur, GA, USA

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

Abbreviations
CDC Centers for Disease Control and Prevention; DAA direct-acting antivirals; HCC hepatocellular carcinoma; HCV hepatitis C virus; IDU injection drug users; NHANES National Health and Nutrition Examination Survey; peg-IFN pegylated interferon; QALY quality-adjusted life year; RBV ribavirin; SOC standard of care; SVR sustained virologic response.

Correspondence
Raymond F. Schinazi, Center for AIDS Research, Emory University School of Medicine and Veterans Affairs Medical Center, Decatur, GA 30033, USA
Tel: +1 404 728 7711
Fax: +1 404 728 7726
e-mail: rschina@emory.edu and lhagan2@emory.edu

DOI:10.1111/liv.12063

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'.

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, multilevel work required to implement such solutions. With the promise of safe, all-oral, direct-acting antiviral (DAA) 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

Hepatitis C virus 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% to 0.1% in parts of the UK and Scandinavia to 15–20% in Egypt (5–8). However, true prevalence is elusive because of 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 caused by cirrhosis and HCC (12). Recent country-specific estimates based on death certificate analyses approximate 3500 HCV-related deaths in France in 2001, 7379 in Egypt in 1999 and 15 000 in the USA 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 with 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 USA, primarily as a result of 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 USA, 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 serosurveillance 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 behaviours and higher HCV prevalence compared with the general population (18). Several European Union (EU) countries have recently strengthened their surveillance systems, although 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 towards 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 behaviours 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 with 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 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 behaviours (29, 32–34). Vertical transmission is also possible, although rare; an estimated 4–7% of babies born to HCV-positive mothers acquire infection (35, 36).

Prevention efforts should address all modes of transmission, although 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, whereas needle exchange programmes 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 USA 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 DAA treatments can work towards 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.

Hepatitis C virus 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 USA 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 anaemia 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 USA 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 in the clinic, 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 analogue 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 analogue 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 non-responders. Similar strategies utilizing protease inhibitors for genotype 1 non-responders 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

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 weeks	15	100	100		(117)
Sofosbuvir + Daclatasvir				14				
Sofosbuvir + Daclatasvir + RBV				15				
Sofosbuvir + Daclatasvir with Sofosbuvir lead-in	2/3	Naïve	24 weeks	16	88	88		
Sofosbuvir + Daclatasvir				14	100	100		
Sofosbuvir + Daclatasvir + RBV				14	86	86		
Sofosbuvir + RBV	1	Naïve	12 weeks	25	88			(64)
				17	59			
ABT-450 + ABT-333 + ABT-267 + Ritonavir + RBV	1	Naïve	12 weeks	79	99	99		(118)
		Null/partial responders (peg-IFN + RBV)		45	93	93		
ABT-450 + ABT-072 + RBV	1a/1b	Naïve	12 weeks	11	100	91	91	(38)
ABT-450 + ABT-333 + RBV	1a/1b	Naïve	12 weeks	33	94	94		(39)
		Null/partial responders (peg-IFN + RBV)		17	47	47		
Daclatasvir + Asunaprevir	1b	Null responders (peg-IFN + RBV)	24 weeks	21	91	91	91	(65)
	1b	Treatment Ineligible/ Intolerant (peg-IFN + RBV)	24 weeks	22	86	64	64	
Daclatasvir + Asunaprevir + BMS-791325	1	Naïve	12 weeks	16	94			(119)
Mericitabine + Ritonavir-boosted Danoprevir + RBV	1a	Naïve	24 weeks	43		26		(120, 121)
	1b	Naïve		21		71		
		Partial responders (peg-IFN + RBV)		23	44			
		Null responders (peg-IFN + RBV)		29	72			
Alisporivir monotherapy	2/3	Naïve	24 weeks	18			72	(122)
Alisporivir + RBV	2/3	Naïve	24 weeks	61			92	(122)
BI 201335 + BI 207127 + RBV	1	Naïve	16 weeks	81	70	59		(123)
			28 weeks	78	76	68		
			40 weeks	77	56	39		

quality-adjusted life years (QALY) gained compared with SOC treatment in genotypes 1, 2 and 3. QALY gained per dollar spent were maximized in younger treatment cohorts because of longer life expectancy and slower disease progression, although the degree of cost-effectiveness of these regimens will depend on 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. Because of 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) *vs* 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 formulation of a single vaccine for all genotypes challenging. 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 USA (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 centre in the USA, 85% were in favour of universal HCV screening during clinician visits. Of those in favour, 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 (80). 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 EU, efforts to improve HCV awareness and testing have increased treatment rates. For example, an HCV prevention programme 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 (81). 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 programmes 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 (82).

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, targeted 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

Injection drug users account for an estimated 40% of known HCV infections in the EU overall, 60% in the USA and up to 97% in England and Wales (5, 83, 84). 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 USA and 81% in Denmark (83–85). 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 (83, 86).

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 USA, 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 (87). Partnering with schools, religious institutions, community and popular media groups, substance abuse treatment programmes, 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 (88). Barriers to HCV treatment among IDU include physicians' concerns about treatment adherence and reinfection as a result of continued drug use, as well as comorbid psychiatric conditions (89). However, numerous studies have demonstrated successful HCV treatment in IDU populations (90–92), especially when enrolment in care is ensured before, during and after a decision to initiate treatment has been made (88). A recent model suggests that treating 40 infections per 1000 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 (93). Furthermore, IDU who have access to needle exchange programmes have shown a reduction in the high-risk needle sharing behaviours that lead to reinfection (94, 95).

Directly observed HCV treatment programmes that are integrated with substance abuse treatment, education, peer support and linkage to tertiary care have shown the greatest success among IDU (90). 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 (88). Thus, providing HCV treatment to IDU in integrated settings such as methadone maintenance clinics can help them manage their drug addictions and comorbid conditions, including alcoholism, which has been associated with accelerated HCV disease progression and mortality (15, 96). In addition, integrated approaches can provide greater continuity of care during treatment, leading to better treatment outcomes and reduced HCV prevalence.

Prison inmates

Hepatitis C virus prevalence in the USA 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 USA (97). Current federal and state laws recommend HCV screening in prisons based on self-reported risk factors, which are vastly underreported because of fear of self-incrimination and distrust of the prison system (98, 99).

Regulations for HCV screening in correctional settings should follow the footsteps of HIV screening, which is offered universally to all inmates in the USA at the time of incarceration (100). Many could then be treated while in prison or referred to care in clinical or community settings when released (97). In a study of prison inmates in the UK, those referred to care after HCV diagnosis demonstrated 100% referral attendance, although referral occurred at a lower rate among inmates compared with 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 because of 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

Hepatitis C virus screening should also leverage the existing infrastructure built for HIV and HBV testing. Partly because of 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 (85, 101). 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 (102–105).

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 USA (85, 106). 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 (85, 101, 107). 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 USA) 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 USA 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 USA for adults in this age group (108). 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 because of it 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 with other modes of transmission like injection drug use, it results in 7500 infected babies each year in the USA, 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% (109, 110).

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, 111). 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 (112).

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 paediatrician), the risk of loss to follow-up is amplified, and continuity of care is especially important. Obstetricians referring infected mothers to HCV 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 (113–115).

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 (111, 116) and is two to three 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 and institutional 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 existing infections and prevent reinfection towards 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 towards 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

Table 2. Summary of recommendations towards HCV eradication

Strategy	Recommendations
Infection identification	• 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	• 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	• Coordinate education on transmission, risk and health consequences of HCV among schools, religious institutions, media outlets, health departments, community centres, clinicians, drug rehabilitation centres 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 programmes to prevent and reduce intimate partner violence and sexual assault, which could become important HCV risk factors
Advocacy	• 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

centres, 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 towards 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 imminent 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.

Disclosure

This work was supported in part by NIH CFAR grant 2P30-AI-050409 (to RFS), the Department of Veterans Affairs (to RFS).

References

1. World Health Organization. Smallpox fact sheet. 2001 Available at http://www.who.int/mediacentre/factsheets/smallpox/en/ Accessed: 24 September 2012.
2. World Health Organization. Poliomyelitis fact sheet. February 2012 Available at http://www.who.int/mediacentre/factsheets/fs114/en/ Accessed: 24 September 2012.
3. World Health Organization. Global burden of disease (GBD) for hepatitis C. *J Clin Pharmacol* 2004; **44**: 20–9.
4. Sherlock DS. Chronic hepatitis C. *Dis Mon* 1994; **40**: 117–96.
5. Alter MJ. Epidemiology of hepatitis C virus infection. *World J Gastroenterol* 2007; **13**: 2436–41.
6. Frank C, Mohamed MK, Strickland GT, *et al.* The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. *Lancet* 2000; **355**: 887–91.
7. Guerra J, Garenne M, Mohamed MK, Fontanet A. HCV burden of infection in Egypt: results from a nationwide survey. *J Viral Hepat* 2012; **19**: 560–7.
8. Esmat G, El Raziky M, El Kassas M, Hassany M, Gamil ME. The future for the treatment of genotype 4 chronic hepatitis C. *Liver Int* 2012; **32**(Suppl. 1): 146–50.
9. Institute of Medicine. *Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C*. Washington, DC: The National Academies Press, 2010.
10. Hatzakis A, Wait S, Bruix J, *et al.* The state of hepatitis B and C in Europe: report from the hepatitis B and C summit conference. *J Viral Hepat* 2011; **18**(Suppl. 1): 1–16.
11. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol* 2006; **45**: 529–38.
12. Averhoff FM, Glass N, Holtzman D. Global burden of hepatitis C: considerations for healthcare providers in the United States. *Clin Infect Dis* 2012; **55**(Suppl. 1): S10–5.
13. Deuffic-Burban S, Mohamed MK, Larouze B, Carrat F, Valleron AJ. Expected increase in hepatitis C-related mortality in Egypt due to pre-2000 infections. *J Hepatol* 2006; **44**: 455–61.
14. Ly KN, Xing J, Klevens RM, *et al.* The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. *Ann Intern Med* 2012; **156**: 271–8.
15. Marcellin P, Pequignot F, Delarocque-Astagneau E, *et al.* Mortality related to chronic hepatitis B and chronic hepatitis C in France: evidence for the role of HIV coinfection and alcohol consumption. *J Hepatol* 2008; **48**: 200–7.
16. El-Kamary SS, Jhaveri R, Shardell MD. All-cause, liver-related, and non-liver-related mortality among HCV-infected individuals in the general US population. *Clin Infect Dis* 2011; **53**: 150–7.
17. United States Department of Health & Human Services. Combating the silent epidemic of viral hepatitis: action plan for the prevention, care & treatment of viral hepatitis. Washington, DC 2011.
18. Chak E, Talal AH, Sherman KE, Schiff ER, Saab S. Hepatitis C virus infection in USA: an estimate of true prevalence. *Liver Int* 2011; **31**: 1090–101.
19. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis* 2005; **5**: 558–67.
20. Hauri AM, Armstrong GL, Hutin YJ. The global burden of disease attributable to contaminated injections given in health care settings. *Int J STD AIDS* 2004; **15**: 7–16.
21. World Health Organization. Blood safety and availability: facts and figures from the 2007 Blood Survey. 2012 Available at http://www.drmahwish.com/publications/blood-safety-and-availability-who/ Accessed: 25 September 2012.
22. Madwar MA, El-Gindy I, Fahmy HM, Shoeb NM, Massoud BA. Hepatitis C virus transmission in family members of Egyptian patients with HCV related chronic liver disease. *J Egypt Public Health Assoc* 1999; **74**: 313–32.
23. de Waure C, Cefalo C, Chiaradia G, *et al.* Intrafamilial transmission of hepatitis C virus in Italy: a systematic review. *J Epidemiol Community Health* 2010; **64**: 843–8.
24. Rooney G, Gilson RJ. Sexual transmission of hepatitis C virus infection. *Sex Transm Infect* 1998; **74**: 399–404.
25. Stroffolini T, Lorenzoni U, Menniti-Ippolito F, Infantolino D, Chiaramonte M. Hepatitis C virus infection in spouses: sexual transmission or common exposure to the same risk factors? *Am J Gastroenterol* 2001; **96**: 3138–41.
26. Marincovich B, Castilla J, del Romero J, *et al.* Absence of hepatitis C virus transmission in a prospective cohort of heterosexual serodiscordant couples. *Sex Transm Infect* 2003; **79**: 160–2.
27. Caporaso N, Ascione A, Stroffolini T. Spread of hepatitis C virus infection within families. Investigators of an Italian Multicenter Group. *J Viral Hepat* 1998; **5**: 67–72.
28. Hajiani E, Masjedizadeh R, Hashemi J, Azmi M, Rajabi T. Hepatis C virus transmission and its risk factors within families of patients infected with hepatitis C virus in southern Iran: khuzestan. *World J Gastroenterol* 2006; **12**: 7025–8.
29. Terrault NA. Sexual activity as a risk factor for hepatitis C. *Hepatology* 2002; **36**(5 Suppl. 1): S99–105.
30. Ghosn J, Leruez-Ville M, Chaix ML. Sexual transmission of hepatitis C virus. *Presse Med* 2005; **34**: 1034–8.
31. Russell M, Chen MJ, Nochajski TH, *et al.* Risky sexual behavior, bleeding caused by intimate partner violence, and hepatitis C virus infection in patients of a sexually transmitted disease clinic. *Am J Public Health* 2009; **99** (Suppl. 1): S173–9.
32. Danta M, Brown D, Bhagani S, *et al.* Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. *AIDS* 2007; **21**: 983–91.
33. Centers for Disease Control and Prevention. Sexual transmission of hepatitis C virus among HIV-infected men who have sex with men–New York City, 2005–2010. *MMWR Morb Mortal Wkly Rep* 2011; **60**: 945–50.
34. Schmidt AJ, Rockstroh JK, Vogel M, *et al.* Trouble with bleeding: risk factors for acute hepatitis C among HIV-positive gay men from Germany–a case-control study. *PLoS ONE* 2011; **6**: e17781.
35. Centers for Disease Control and Prevention, Division of Viral Hepatitis. Hepatitis C FAQs for health professionals. 2012 Available at http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm. Accessed: 22 July 2012.
36. Mack CL, Gonzalez-Peralta RP, Gupta N, *et al.* NASPGHAN practice guidelines: diagnosis and management of hepatitis C infection in infants, children, and adolescents. *J Pediatr Gastroenterol Nutr* 2012; **54**: 838–55.
37. Centers for Disease Control and Prevention. Progress toward prevention and control of hepatitis C virus infection–Egypt, 2001-2012. *MMWR Morb Mortal Wkly Rep* 2012; **61**: 545–9.

38. Lawitz E, Poordad F, Kowdley K, *et al.* A 12-week interferon-free regimen of ABT-450/r, ABT-072, and ribavirin was well tolerated and achieved sustained virologic response in 91% treatment-naive IL28B-CC genotype infected subject. In: The International Liver Congress, 47th Annual Meeting of the European Association for the Study of the Liver. Barcelona, Spain, 2012.
39. Poordad F, Lawitz E, Kowdley K, *et al.* 12-week interferon-free regimen of ABT-450/R+ABT-333 + ribavirin achieved SVR12 in more than 90% of treatment-naive HCV genotype-1-infected subjects and 47% of previous non-responders. In: The International Liver Congress, 47th Annual Meeting of the European Association for the Study of the Liver. Barcelona, Spain, 2012.
40. Sulkowski M, Gardiner D, Lawitz E, *et al.* Potent viral suppression with the all-oral combination of daclatasvir (NS5A inhibitor) and GS-7977 (nucleoside NS5B inhibitor), ± ribavirin, in treatment-naive patients with chronic HCV GT1, 2, or 3 (100% SVR gt1, 91% gt2) In: The International Liver Congress, 47th Annual Meeting of the European Association for the Study of the Liver. Barcelona, Spain, 2012.
41. Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. *Clin Infect Dis* 2011; **52**: 889–900.
42. Alter HJ, Liang TJ, Hepatitis C. The end of the beginning and possibly the beginning of the end. *Ann Intern Med* 2012; **156**: 317–8.
43. Manns MP, McHutchison JG, Gordon SC, *et al.* Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; **358**: 958–65.
44. Antaki N, Hermes A, Hadad M, *et al.* Efficacy of interferon plus ribavirin in the treatment of hepatitis C virus genotype 5. *J Viral Hepat* 2008; **15**: 383–6.
45. Nguyen NH, VuTien P, Garcia RT, *et al.* Response to pegylated interferon and ribavirin in Asian American patients with chronic hepatitis C genotypes 1 vs 2/3 vs 6. *J Viral Hepat* 2010; **17**: 691–7.
46. Zhou YQ, Wang XH, Hong GH, *et al.* Twenty-four weeks of pegylated interferon plus ribavirin effectively treat patients with HCV genotype 6a. *J Viral Hepat* 2011; **18**: 595–600.
47. Khattab MA, Ferenci P, Hadziyannis SJ, *et al.* Management of hepatitis C virus genotype 4: recommendations of an international expert panel. *J Hepatol* 2011; **54**: 1250–62.
48. Asselah T, De Muynck S, Broet P, *et al.* IL28B polymorphism is associated with treatment response in patients with genotype 4 chronic hepatitis C. *J Hepatol* 2012; **56**: 527–32.
49. National Institutes of Health. NIH Consensus Statement on Management of Hepatitis C. *NIH Consensus State-of-the-Science Statements* 2002; **19**: 1–46.
50. McHutchison JG, Lawitz EJ, Shiffman ML, *et al.* Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009; **361**: 580–93.
51. Gupta S, Singh R. Analysis of the virus dynamics model reveals that early treatment of HCV infection may lead to the sustained virological response. *PLoS ONE* 2012; **7**: e41209.
52. Hsu CS, Kao JH. Genomic variation-guided management in chronic hepatitis C. *Expert Rev Gastroenterol Hepatol* 2012; **6**: 497–506.
53. Poordad F, Bronowicki JP, Gordon SC, *et al.* Factors that predict response of patients with hepatitis C virus infection to boceprevir. *Gastroenterology* 2012; **143**: 608–18 e5.
54. Bini EJ, Brau N, Currie S, *et al.* Prospective multicenter study of eligibility for antiviral therapy among 4,084 U.S. veterans with chronic hepatitis C virus infection. *Am J Gastroenterol* 2005; **100**: 1772–9.
55. Delwaide J, El Saouda R, Gerard C, Belaiche J. Hepatitis C infection: eligibility for antiviral therapies. *Eur J Gastroenterol Hepatol* 2005; **17**: 1185–9.
56. Doucette KE, Robson V, Shafran S, Kunimoto D. Improving access to care by allowing self-referral to a hepatitis C clinic. *Can J Gastroenterol* 2009; **23**: 421–4.
57. Morrill JA, Shrestha M, Grant RW. Barriers to the treatment of hepatitis C. Patient, provider, and system factors. *J Gen Intern Med* 2005; **20**: 754–8.
58. Niederau C, Huppe D, Zehnter E, *et al.* Chronic hepatitis C: treat or wait? Medical decision making in clinical practice. *World J Gastroenterol* 2012; **18**: 1339–47.
59. Butt AA, Justice AC, Skanderson M, *et al.* Rate and predictors of treatment prescription for hepatitis C. *Gut* 2007; **56**: 385–9.
60. McGowan CE, Fried MW. Barriers to hepatitis C treatment. *Liver Int* 2012; **32**(Suppl. 1): 151–6.
61. Putka B, Mullen K, Birdi S, Merheb M. The disposition of hepatitis C antibody-positive patients in an urban hospital. *J Viral Hepat* 2009; **16**: 814–21.
62. Irving WL, Smith S, Cater R, *et al.* Clinical pathways for patients with newly diagnosed hepatitis C - what actually happens. *J Viral Hepat* 2006; **13**: 264–71.
63. Wagner G, Ryan G, Osilla KC, *et al.* Treat early or wait and monitor? A qualitative analysis of provider hepatitis C virus treatment decision-making in the context of HIV coinfection. *AIDS Patient Care STDS* 2009; **23**: 715–25.
64. Gane E, Stedman C, Hyland R, *et al.* ELECTRON: Once daily PSI-7977 plus RBV in HCV GT1/2/3. In: The International Liver Congress, 47th Annual Meeting of the European Society for the Study of the Liver. Barcelona, Spain, 2012.
65. Suzuki F, Ikeda K, Toyota J, *et al.* Dual oral therapy with the NS5A inhibitor daclatasvir (BMS-790052) and NS3 protease inhibitor (BMS-650032) in HCV genotype 1b-infected null responders or ineligible/intolerant to peginterferon/ribavirin. In: The International Liver Congress, 47th Annual Meeting of the European Association for the Study of the Liver. Barcelona, Spain, 2012.
66. Thomas DL. Advances in the treatment of hepatitis C virus infection. *Top Antivir Med* 2012; **20**: 5–10.
67. Schinazi RF, Bassit L, Gavegnano C. HCV drug discovery aimed at viral eradication. *J Viral Hepat* 2010; **17**: 77–90.
68. Liu S, Cipriano LE, Holodniy M, Owens DK, Goldhaber-Fiebert JD. New protease inhibitors for the treatment of chronic hepatitis C: a cost-effectiveness analysis. *Ann Intern Med* 2012; **156**: 279–90.
69. Hagan LM, Yang Z, Schinazi RF. Cost-effectiveness of all-oral, interferon-free treatment for chronic hepatitis C. In: Bridging the Sciences S2E-HCV Workshop: Seek, Test, Treat, Eradicate HCV. Atlanta, GA, 2012.

70. Roohvand F, Kossari N. Advances in hepatitis C virus vaccines, part two: advances in hepatitis C virus vaccine formulations and modalities. *Expert Opin Ther Pat* 2012; **22**: 391–415.
71. Grebely J, Prins M, Hellard M, *et al.* Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of injecting drug users: towards a vaccine. *Lancet Infect Dis* 2012; **12**: 408–14.
72. Ip PP, Nijman HW, Wilschut J, Daemen T. Therapeutic vaccination against chronic hepatitis C virus infection. *Antiviral Res* 2012; **96**: 36–50.
73. Lambotin M, Barth H, Moog C, *et al.* Challenges for HCV vaccine development in HIV-HCV coinfection. *Expert Rev Vaccines* 2012; **11**: 791–804.
74. World Health Organization. Initiative for vaccine research, viral cancers, hepatitis C virus. 2010 Available at http://www.who.int/vaccine_research/diseases/viral_cancers/en/index2.html. Accessed: 27 September 2012.
75. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009; **49**: 1335–74.
76. Armstrong GL, Wasley A, Simard EP, *et al.* The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med* 2006; **144**: 705–14.
77. Coffin PO, Stevens AM, Scott JD, Stekler JD, Golden MR. Patient acceptance of universal screening for hepatitis C virus infection. *BMC Infect Dis* 2011; **11**: 160.
78. Wong JB, McQuillan GM, McHutchison JG, Poynard T. Estimating future hepatitis C morbidity, mortality, and costs in the United States. *Am J Public Health* 2000; **90**: 1562–9.
79. Rein DB, Smith BD, Wittenborn JS, *et al.* The cost-effectiveness of birth-cohort screening for hepatitis C antibody in U.S. primary care settings. *Ann Intern Med* 2012; **156**: 263–70.
80. Singer ME, Younossi ZM. Cost effectiveness of screening for hepatitis C virus in asymptomatic, average-risk adults. *Am J Med* 2001; **111**: 614–21.
81. Delarocque-Astagneau E, Meffre C, Dubois F, *et al.* The impact of the prevention programme of hepatitis C over more than a decade: the French experience. *J Viral Hepat* 2010; **17**: 435–43.
82. Morano J, Gibson B, Altice F. Correlates of HIV, HCV, and HIV/HCV co-infection in a Northeastern inner city population. In: The Liver Meeting, 63rd Annual Meeting of the America Association for the Study of Liver Diseases. Boston, MA, 2012.
83. Sutton AJ, Edmunds WJ, Gill ON. Estimating the cost-effectiveness of detecting cases of chronic hepatitis C infection on reception into prison. *BMC Public Health* 2006; **6**: 170.
84. Weissing L, Roy K, Sapinho D, *et al. Surveillance of Hepatitis C Infection Among Injecting Drug Users in the European Union*. Luxembourg: European Monitoring Centre for Drugs and Drug Addiction; 2006.
85. Centers for Disease Control and Prevention. IDU HIV Prevention: Hepatitis C virus and HIV coinfection. 2002 Available at http://www.cdc.gov/idu/hepatitis/hepc_and_hiv_co.pdf. Accessed: 26 September 2012.
86. Schlicting EG, Johnson ME, Brems C, *et al.* Validity of injecting drug users' self report of hepatitis A, B, and C. *Clin Lab Sci* 2003; **16**: 99–106.
87. Centers for Disease Control and Prevention. Hepatitis C virus infection among adolescents and young adults: Massachusetts, 2002–2009. *MMWR Morb Mortal Wkly Rep* 2011; **60**: 537–41.
88. Grebely J, Genoway K, Khara M, *et al.* Treatment uptake and outcomes among current and former injection drug users receiving directly observed therapy within a multidisciplinary group model for the treatment of hepatitis C virus infection. *Int J Drug Policy* 2007; **18**: 437–43.
89. Edlin BR, Seal KH, Lorvick J, *et al.* Is it justifiable to withhold treatment for hepatitis C from illicit-drug users? *N Engl J Med* 2001; **345**: 211–5.
90. Litwin AH, Soloway I, Gourevitch MN. Integrating services for injection drug users infected with hepatitis C virus with methadone maintenance treatment: challenges and opportunities. *Clin Infect Dis* 2005; **40**(Suppl. 5): S339–45.
91. Matthews G, Kronborg IJ, Dore GJ. Treatment for hepatitis C virus infection among current injection drug users in Australia. *Clin Infect Dis* 2005; **40**(Suppl. 5): S325–9.
92. Mauss S, Berger F, Goelz J, Jacob B, Schmutz G. A prospective controlled study of interferon-based therapy of chronic hepatitis C in patients on methadone maintenance. *Hepatology* 2004; **40**: 120–4.
93. Martin NK, Vickerman P, Foster GR, *et al.* Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. *J Hepatol* 2011; **54**: 1137–44.
94. Bluthenthal RN, Kral AH, Gee L, Erringer EA, Edlin BR. The effect of syringe exchange use on high-risk injection drug users: a cohort study. *AIDS* 2000; **14**: 605–11.
95. Watters JK, Estilo MJ, Clark GL, Lorvick J. Syringe and needle exchange as HIV/AIDS prevention for injection drug users. *JAMA* 1994; **271**: 115–20.
96. Freeman AJ, Dore GJ, Law MG, *et al.* Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology* 2001; **34**(4 Part 1): 809–16.
97. Spaulding AC, Thomas DL. Screening for HCV infection in jails. *JAMA* 2012; **307**: 1259–60.
98. Macalino GE, Dhawan D, Rich JD. A missed opportunity: hepatitis C screening of prisoners. *Am J Public Health* 2005; **95**: 1739–40.
99. Federal Bureau of Prisons. Clinical practice guidelines, evaluation and treatment of hepatitis C and cirrhosis. May 2012.
100. Federal Bureau of Prisons. Clinical practice guidelines, management of HIV. June 2011.
101. Centers for Disease Control and Prevention. Viral hepatitis populations: HIV/AIDS and viral hepatitis. 2012 Available at http://www.cdc.gov/hepatitis/Populations/hiv.htm Accessed: 26 September 12012.
102. Pramoolsinsap C, Sirikulchayanonta V, Busakorn W, *et al.* Coinfections with hepatitis g and/or c virus in hepatitis B-related chronic liver disease. *Southeast Asian J Trop Med Public Health* 1999; **30**: 741–9.
103. Sato S, Fujiyama S, Tanaka M, *et al.* Coinfection of hepatitis C virus in patients with chronic hepatitis B infection. *J Hepatol* 1994; **21**: 159–66.
104. Brown J, Dourakis S, Karayiannis P, *et al.* Seroprevalence of hepatitis C virus nucleocapsid antibodies in patients with cryptogenic chronic liver disease. *Hepatology* 1992; **15**: 175–9.

105. Riezu-Boj JI, Parker D, Civeira MP, *et al.* Detection of hepatitis C virus antibodies with new recombinant antigens: assessment in chronic liver diseases. *J Hepatol* 1992; **15**: 309–13.
106. Bica I, McGovern B, Dhar R, *et al.* Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clin Infect Dis* 2001; **32**: 492–7.
107. Lesens O, Deschenes M, Steben M, Belanger G, Tsoukas CM. Hepatitis C virus is related to progressive liver disease in human immunodeficiency virus-positive hemophiliacs and should be treated as an opportunistic infection. *J Infect Dis* 1999; **179**: 1254–8.
108. Centers for Disease Control and Prevention. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR Recomm Rep* 2012; **61**: 1–32.
109. Stoszek SK, Abdel-Hamid M, Narooz S, *et al.* Prevalence of and risk factors for hepatitis C in rural pregnant Egyptian women. *Trans R Soc Trop Med Hyg* 2006; **100**: 102–7.
110. Shebl FM, El-Kamary SS, Saleh DA, *et al.* Prospective cohort study of mother-to-infant infection and clearance of hepatitis C in rural Egyptian villages. *J Med Virol* 2009; **81**: 1024–31.
111. Valladares G, Chacaltana A, Sjogren MH. The management of HCV-infected pregnant women. *Ann Hepatol* 2010; **9**(Suppl.): 92–7.
112. Sheikh SM. Hepatitis B and C: value of universal antenatal screening. *J Coll Physicians Surg Pak* 2009; **19**: 179–82.
113. Kuhn L, Aldrovandi GM, Sinkala M, *et al.* Potential impact of new WHO criteria for antiretroviral treatment for prevention of mother-to-child HIV transmission. *AIDS* 2010; **24**: 1374–7.
114. Townsend CL, Cortina-Borja M, Peckham CS, *et al.* Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000–2006. *AIDS* 2008; **22**: 973–81.
115. Fitzgerald FC, Bekker LG, Kaplan R, *et al.* Mother-to-child transmission of HIV in a community-based antiretroviral clinic in South Africa. *S Afr Med J* 2010; **100**: 827–31.
116. Madurga Revilla P, Aguar Carrascosa M, Pereda Perez A, *et al.* Retrospective study of risk factors of vertical transmission of hepatitis C virus. *An Pediatr (Barc)* 2012; **76**: 336–42.
117. Sulkowski M, Gardiner D, Rodriguez-Torres M, *et al.* High rate of sustained virologic response with the all-oral combination of Daclatasvir (NS5A inhibitor) plus Sofosbuvir (nucleotide NS5B inhibitor), with or without Ribavirin, in treatment-naive patients chronically infected with HCV genotype 1, 2, or 3. In: *The Liver Meeting, 63rd Annual Meeting of the American Association for the Study of Liver Diseases*, Boston, MA, 2012.
118. Kowdley K, Lawitz E, Poordad F, *et al.* A 12-week interferon-free treatment regimen with ABT-450/r, ABT-267, ABT-333 and Ribavirin achieves SVR12 rates (observed data) of 99% in treatment-naive patients and 93% in prior null responders with HCV genotype 1 infection. In: *The Liver Meeting, 63rd Annual Meeting of the American Association for the Study of Liver Diseases*, Boston, MA, 2012.
119. Everson G, Sims K, Rodriguez-Torres M, *et al.* An interferon-free, ribavirin-free 12-week regimen of Daclatasvir, Asunaprevir, and BMS-791325 yielded SVR4 of 94% in treatment-naive patients with genotype 1 chronic HCV infection. In: *The Liver Meeting, 63rd Annual Meeting of the American Association for the Study of Liver Diseases*, Boston, MA, 2012.
120. Gane E, Pockros P, Zeuzem S, *et al.* Interferon-free treatment with a combination of mericitabine and danoprevir/r with or without ribavirin in treatment-naive HCV genotype 1-infected patients. In: *The International Liver Congress, 47th Annual Meeting of the European Society for the Study of the Liver*, Barcelona, Spain, 2012.
121. Field J, Jacobson I, Jensen D, *et al.* Up to 100% SVR4 rates with ritonavir-boosted danoprevir, mericitabine, and ribavirin plus or minus peginterferon alfa-2a (40KD) in HCV genotype 1-infected partial and null responders: results from the MATTERHORN study. In: *The Liver Meeting, 63rd Annual Meeting of the American Association for the Study of Liver Diseases*, Boston, MA, 2012.
122. Pawlotsky J, Sarin S, Foster G, *et al.* Alisporivir plus Ribavirin achieves high rates of sustained HCV clearance (SVR24) as interferon (IFN)-free or IFN-add-on regimen in treatment-naive patients with HCV GT2 or GT3: final results from VITAL-1 study. In: *The Liver Meeting, 63rd Annual Meeting of the American Association for the Study of Liver Diseases*, Boston, MA, 2012.
123. Zeuzem S, Soriano V, Asselah T, *et al.* SVR4 and SVR12 with an interferon-free regimen of B1201335 and B1207127, ± ribavirin, in treatment-naive patients with chronic genotype 1 HCV infection: Interim results of SOUND-C2. In: *The International Liver Congress, 47th Annual Meeting of the European Society for the Study of the Liver*, Barcelona, Spain, 2012.