Review

Treatment as prevention and cure towards global eradication of hepatitis C virus

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The availability of curative, direct-acting antiviral drugs against hepatitis C virus (HCV) sparks an ethical call for HCV eradication and provides essential tools to spearhead the effort. Challenges include increasing awareness of the chronic hepatitis C epidemic, garnering sufficient public, private, and governmental financial will to invest in the necessary resources, developing pangenotypic drug regimens for global application, and mitigating ethical concerns. To achieve these goals, stakeholders including clinicians, public health professionals, legislators, advocates, and industry can employ a variety of strategies such as increasing HCV screening, implementing treatment as prevention, and improving linkage to care, as well as developing innovative pricing and payment solutions, stimulating innovation through local drug development in high-prevalence regions, continuing vaccine development, and creating efficiencies in the marketing and distribution of educational materials and drug treatments.

Burden of disease and curative therapy for HCV

Approximately 150 million people worldwide and 3.2 million in the USA live with chronic hepatitis C infection (CHC), which frequently progresses, largely asymptomatically, to cirrhosis and/or liver cancer over the course of 20–30 years, conferring increased risk of premature death (World Health Organization, http://www.who.int/mediacentre/factsheets/fs164/en/index.html; Centers for Disease Control and Prevention, http://www.cdc.gov/hepatitis/hcv/hcvfaq.htm) [1]. Although an estimated 75% of individuals in the USA infected with HCV and up to 90% in parts of the European Union are unaware of their status (US Department of Health and Human Services, http://www.hhs.gov/ash/initiatives/hepatitis/actionplan_viralhepatitis2011.pdf) [2], recent screening enhancements are expected to gradually reduce the number of undiagnosed cases [3]. Even once diagnosed, however, many infected individuals have postponed treatment with standard-of-care interferon-based regimens, awaiting more effective oral options with fewer side effects (http://www.hhs.gov/ash/initiatives/hepatitis/actionplan_viralhepatitis2011.pdf).

A 24-week regimen of pegylated interferon and ribavirin results in a sustained virologic response (SVR, see Glossary) for 75–80% of non-cirrhotic individuals with genotype 2, 3, 5, and 6 infections. Extending treatment duration to 48 weeks has yielded up to 70% SVR for genotype 4, but only 42% for genotype 1. For all genotypes, this treatment causes debilitating side effects including depression, anemia, and flu-like symptoms [4–11]. Adding a protease inhibitor (either telaprevir or boceprevir) can boost genotype 1 SVR to 72%, but also adds the risk of further adverse events (Merck & Co., http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202258lbl.pdf; Vertex Pharmaceuticals, http://pi.vrtx.com/files/uspi_telaprevir.pdf). In advanced clinical trials, the most promising treatments to date – all-oral, interferon-free regimens of direct-acting antiviral (DAA) drugs – have achieved SVR in 90%+ of genotype 1–4-infected individuals and show promise for genotypes 5 and 6, without the side effects associated with interferon [12–16].

With FDA approval complete or imminent for several of these DAA-based drug regimens including the Gilead sofosbuvir plus ribavirin combination (http://www.gilead.com/news/press-releases/2013/10/fda-advisory-committee-supports-approval-of-gileads-sofosbuvir-for-chronic-hepatitis-c-infection) and the AbbVie triple DAA plus ribavirin/protease booster combination (http://abbvie.mediaroom.com/2013-05-06-AbbVies-investigational-HCV-regimen-receives-breakthrough-therapy-designation-from-the-U-S-Food-and-Drug-Administration), all-oral treatment with SVR rates approaching 100% will soon be available in the

Glossary

Incremental cost-effectiveness ratio (ICER): compares the costs of two different treatments and the quality-adjusted life years (QALY) gained by using them over a specified time period in a cohort of subjects. Defined as (cost of treatment 1 – cost of treatment 2)/(QALY gained with treatment 1 – QALY gained with treatment 2).
Pangenotypic HCV treatment: antiviral agent/combination that is effective against all HCV genotypes.
Sustained virologic response (SVR): lack of detectable HCV RNA in the blood at a specified time after completion of antiviral treatment; at this time, SVR 12 weeks after treatment is the standard definition of a cure for HCV.
Treatment-experienced individuals: HCV-positive individuals who have been treated previously but have not achieved SVR.

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Box 1. Outstanding questions

- How long will it take for the most effective HCV treatments to become available at low cost, and how can advocates and governments work with drug manufacturers to increase access as soon as possible?
- In addition to working with industry, what can local governments do to leverage drug access for their own HCV-positive populations?
- Can pilot eradication studies be initiated in a small country (such as Georgia, for example) to evaluate the ability of a powerful and safe pangenotypic DAA combination to eradicate HCV in a defined population?
- How can Western governments encourage pharmaceutical companies to balance profit expectations with compassionate use, considering the fact that a large proportion of HCV-infected individuals come from low-income or marginalized groups unable to afford treatment at expected market-entry prices?
- How can stakeholders promote early treatment and treatment as prevention and cure?
- How short can treatment be and still achieve a cure in treatment-naïve, treatment-experienced, and difficult-to-treat individuals with HCV?
- Can a suboptimal dose of an antiviral agent be used prophylactically in high-risk individuals to prevent reinfection after cure without selecting for resistant viruses?
- Can novel DAA regimens be used safely during pregnancy to prevent vertical transmission from an infected mother to her baby? Can they be used safely and effectively in children aged 0–18 years?
- What creative strategies can be deployed with industry partners to optimize screening access, treatment distribution, and adherence?

clinic. These drugs will likely end the search for curative therapy for genotype 1 infection, which accounts for 60% of cases globally (http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/index2.html). However, more work is necessary to develop pangenotypic treatments and to make the most effective drugs financially accessible to all who need them as both prevention and cure. Achieving these goals will transform HCV eradication from a distant ideal to an actionable, strategic possibility (Box 1).

Ethics of HCV eradication

The two global disease eradication success stories to date, smallpox (declared eradicated in 1980, http://www.who.int/features/2010/smallpox/en/index.html) and polio (now endemic in only a handful of countries, http://www.polioeradication.org/portals/0/document/resources/strategywork/economiccase.pdf), have featured infections resulting from single, identified etiologic agents and have focused on prevention through vaccination and containment. Prior to intensified eradication efforts, smallpox and polio infected 50 million and 350 000 people, respectively, worldwide each year (http://www.polioeradication.org/Portals/0/Document/Resources/StrategyWork/EconomicCase.pdf) [17], compared to 150 million currently afflicted with CHC (although acute HCV incidence remains elusive). Like smallpox and polio, HCV infection results from a single known virus. Although there is not yet a vaccine that can prevent HCV infection, drug therapy can cure existing cases, providing a tool that was unavailable in previous eradication campaigns.

Now that a very high rate of cure is possible with DAA drug combinations, a coordinated global HCV eradication campaign has become a moral imperative. However, such a campaign will differ from its vaccination-based predecessors, and these differences present several challenges. Whereas vaccination can be applied universally, curative efforts require identification of specific infected individuals through screening. Mass medical screening introduces its own ethical questions, since false positives can lead to psychological stress and unnecessary treatment, and false negatives to further disease progression and unwitting transmission. Positive test results, whether true or false, can also carry potentially detrimental implications for family relationships, employment, and insurance status. In addition, obtaining informed consent for screening for an asymptomatic condition such as CHC could be challenging, and incentives to encourage screening should be carefully set at levels that minimize coercion [18], especially in regions where the motives of external medical interventions can be considered suspect. Mitigating the potential harms and complications of mass screening for HCV must be part of the plan for any eradication campaign.

HCV control and prevention efforts to date have focused on reducing transmission through behavioral interventions including safe injection practices in healthcare settings and reducing needle sharing among injection drug users [19]. The double benefit of curative treatment lies in its ability to serve as both individual cure and future prevention, supplementing behavioral control efforts for an even more powerful effect. A recent model developed by Montaner *et al.* illustrates that effective CHC treatment prevents future incident HCV cases by reducing the number of transmitters, eventually stifling the epidemic [20], just as HIV treatment has proven to be a successful prevention strategy in a variety of settings [21,22]. Treatment as prevention and cure can form the backbone of eradication strategies provided that there is sufficient financial will from the public, industry, and governmental bodies to deploy the necessary resources.

Ultimately, eradication will require both treatments and vaccines, and development efforts for vaccination as treatment and prophylaxis are ongoing [23–26]. Once effective vaccines have been developed, local health departments can partner with pharmaceutical companies, clinicians, media organizations, and advocacy groups to implement vaccination campaigns to strengthen the eradication efforts begun with curative therapy and to prevent reinfection among high-risk individuals who have been cured with novel DAA drugs.

The amount of public and private funding dedicated to disease eradication is often proportional not to the actual incidence and prevalence of the disease in question, but instead to its visibility, as well as the public's perceived risk of infection and ability to identify with its victims. Whereas polio and smallpox result in acute visible symptoms soon after infection, CHC progresses gradually and often asymptomatically over the course of 20–30 years, leaving mostly internal scars [27]. In general, there is low public awareness of the modes of HCV transmission, its progression, prevalence, means of diagnosis, treatment options, and its connection to liver cancer and serious medical interventions such as liver transplants [27–29]. There is no coherent social community rallying around HCV advocacy efforts as there is for HIV/AIDS, nor are

there many well-known HCV-positive individuals to help build a public identity for HCV similar to that of HIV/AIDS today or polio during the 1950s. Furthermore, the burden of CHC in developed countries is disproportionately borne by marginalized populations including injection drug users and homeless and incarcerated individuals [30], and transmission is associated with socially stigmatized behavior that may portray those infected as morally culpable. Compared to the public outcry to eradicate polio and smallpox, there has been barely a murmur calling for systematic action to undermine the silent epidemic of CHC, which generates few headlines. For these reasons, HCV eradication will be daunting. However, with a cure in sight, inaction is not an option.

Paying for a cure

All-oral HCV drugs on the horizon are expected to be cost-effective compared to standard-of-care interferon-based treatments [31]. Although cost-effectiveness analysis can help in determining whether, for a generalized payer, the benefits of all-oral treatment are worth their financial costs on an aggregate level, it does not evaluate who will pay for these drugs and under what circumstances, or whether they will be affordable for those who need them. With all-oral regimens projected to match the US$70 000 cost of current standard-of-care treatment for genotype 1 infection (triple therapy with pegylated interferon, ribavirin, and telaprevir or boceprevir) [32], or even to eclipse that figure if the approved regimens ultimately include more than one DAA, the final price set in the USA and other developed countries will exceed the ability to pay for many individuals and will likely be completely out of reach for most of the developing world.

Although vaccination-based eradication campaigns require a great deal of resources at the population level, the cost to the individual is low and is often funded by governments, non-governmental organizations (NGOs), or private insurance. An estimated 2.5 billion children have been vaccinated against polio over the past 20 years for as little as US$0.11 per vaccination (http://www.who.int/features/factfiles/polio/facts/en/index4.html). By contrast, the staggering cost of HCV treatment is often borne by the individual, preventing universal access. The cost of curative therapy will be the most significant barrier to HCV eradication, and surmounting it will require collaboration among healthcare providers, drug manufacturers, local and national governments, and other key players.

Access to treatment

High drug costs are not a new phenomenon. Treatments that delay cancer-related mortality by only a few months can cost tens of thousands of dollars [33,34], and HIV-infected individuals face a lifetime of antiretroviral therapy averaging over $12 000 per year in the USA (National Alliance of State and Territorial AIDS Directors, http://nastad.org/docs/NASTAD-National-ADAP-Monitoring-Project-Report-Module-1-2013-1.pdf). In comparison, $70 000 for drugs that could extend the life of a HCV-infected person for decades and save hundreds of thousands of dollars in downstream medical costs could seem like a reasonable tradeoff. Regardless of these comparisons, however, the question of access remains. One-quarter of HCV-positive individuals in the USA included in the Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES) between 2001 and 2008 reported being uninsured [35], and despite the universal insurance coverage mandate put in place by the US Patient Protection and Affordable Care Act in 2010, many low-income families without coverage could be ineligible for federal insurance subsidies and remain uninsured.

HCV-infected people living in lower-income countries have even fewer options, and curative drugs are financially inaccessible for all except the wealthiest citizens. A 2011 report by the Eurasian Harm Reduction Network identified price as the primary barrier to current standard-of-care interferon-based HCV treatment in Eastern Europe and Central Asia (http://www.idhdp.com/media/33100/ehrn_hepatitis_c_treatment_access_in_eeca.pdf). In these countries, a full course of pegylated interferon alone costs between $10 000 and $20 000 per person. When governments and individuals are unable to finance these comparatively inexpensive treatments, the prospects for access to more efficacious and expensive drug regimens such as the DAA drugs mentioned above are bleak.

Effective treatment-based HCV eradication, particularly for genotype 1 infections, will not be possible without access to these advanced drugs. A multi-faceted strategy is needed to advance universal CHC treatment towards global eradication, and assistance from public sources and pharmaceutical companies will play essential roles in helping HCV-infected individuals in low-income groups and low-resource countries afford a cure.

The role of public funding

In the USA, a limited amount of government-funded HCV prescription assistance is available for low-income, uninsured/underinsured individuals with HIV co-infection through state-based AIDS Drug Assistance Programs (ADAPs), a 'payer of last resort' funded by the Ryan White Comprehensive Resources Emergency Act. However, because ADAPs exist primarily to provide resources for HIV treatment and their funding is vulnerable to cuts in the discretionary spending of individual states, only a small portion is available for HCV medications. In 2011, the national ADAP budget was $1.88 billion, allocated from a variety of state and federal sources. The 20 states whose ADAPs covered HCV treatment that year filled 3640 HCV prescriptions to serve co-infected individuals over the full course of the year, compared to 449 154 HIV-related prescriptions overall in the month of June 2012 alone (National Alliance of State and Territorial AIDS Directors, http://nastad.org/docs/NASTAD-National-ADAP-Monitoring-Project-Report-Module-1-2013-1.pdf). The disparity between these 3640 HCV prescriptions filled and the likely 3.2 million HCV-infected individuals in the USA (Centers for Disease Control and Prevention, http://www.cdc.gov/hepatitis/hcv/hcvfaq.htm), approximately 90% of whom are not co-infected with HIV [36], illustrates a wide gap in services. This gap, coupled with the expectation of rising CHC-related medical costs and productivity losses as many infected individuals progress to end-stage liver disease

[37–39], represents a compelling case for additional public funding for HCV prescription assistance in the USA.

In a 2010 World Hepatitis Alliance/World Health Organization (WHO) study of viral hepatitis policy in 135 WHO member states, 69% of countries (83%, 77%, and 33% of high-, middle-, and low-income countries, respectively) reported provision of some form of public funding for treatment of hepatitis B and/or C. (The allocation specifically for HCV was not reported.) According to this report, 41% of the world's population lives in countries where no public funding is available for treatment (http://www.who.int/immunization/topics/hepatitis_b_survey_2010/en/). Some governments in addition to the USA have linked public funding for HCV treatment to HIV co-infection. For example, Georgia and the Ukraine have made successful requests to the World Bank and the Global Fund to Fight AIDS, Tuberculosis, and Malaria for resources to provide HCV treatment for their HIV co-infected populations, but provide little funding to treat other HCV-infected groups (http://www.idhdp.com/media/33100/ehrn_hepatitis_c_treatment_access_in_eeca.pdf). With up to 20% of HCV-infected individuals eventually developing end-stage liver disease (Centers for Disease Control and Prevention, http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm) and incurring annual medical costs in the USA between $30 000 and $70 000 to treat cirrhosis and liver cancer and up to $350 000 for a liver transplant [40–42], the societal costs of non-treatment are continually mounting.

HIV/AIDS advocates have successfully garnered public support to help finance necessary antiretroviral treatment for some of the most vulnerable of the 1.1 million people in the USA living with HIV (Centers for Disease Control and Prevention, http://www.cdc.gov/hiv/library/reports/surveillance/2011/surveillance_Report_vol_23.html). However, because CHC is asymptomatic until late stages of disease, it does not have the same level of visibility to the public or to legislators and has received less budgetary attention globally compared to HIV. The existing federal and state funds available in the USA for HCV prescriptions through ADAPs, as well as international aid procured to treat co-infected individuals in lower-income countries, provide a foot in the door to emphasize the growing burden of CHC, to broaden eligibility for publicly funded prescription assistance beyond HIV co-infected individuals, and to make HCV treatment more accessible for low-income populations in the USA and worldwide.

The role of industry

HIV/AIDS also provides a useful illustration of effective industry-based treatment assistance programs. Some of the success of programs such as ADAP and the President's Emergency Plan for AIDS Relief (PEPFAR) hinges on negotiated price reductions and rebates from drug manufacturers. In 2012, ADAP estimated that it received $736 million in drug rebates, a figure equal to one-third of its $2.2 billion total operating budget for 2012 (National Alliance of State and Territorial AIDS Directors, http://nastad.org/docs/NASTAD-National-ADAP-Monitoring-Project-Report-Module-1-2013-1.pdf).

Pharmaceutical companies also offer assistance programs directly to HIV-infected individuals, sometimes covering up to $500 per month per prescription [43]. Compared to these programs, which subsidize drug costs for a lifetime of antiretroviral therapy, HCV prescription assistance programs could be less expensive for drug companies because of the short duration of one-time, all-oral HCV treatment regimens (8–12 weeks, or up to 24 weeks for individuals who are more difficult to treat, including those with cirrhosis). However, short treatment duration may reduce the long-term profitability of these drugs overall.

Governments can also leverage drug discounts and have successfully done so for standard-of-care HCV medications. As detailed above, the government purchase price for pegylated interferon varies by $10 000 or more per course of treatment across countries in Eastern Europe and Central Asia, due in part to large volume purchase commitments by some countries. For example, once the Georgian government began to cover HCV treatment for individuals co-infected with HIV with support from the Global Fund to Fight AIDS, Tuberculosis, and Malaria, it was able to negotiate a price for pegylated interferon that was one-third of what neighboring Kazakhstan paid for the same medication (http://www.idhdp.com/media/33100/ehrn_hepatitis_c_treatment_access_in_eeca.pdf).

It is likely that the success of HCV eradication efforts will depend on the willingness of pharmaceutical companies to provide similar rebates and negotiate affordable prices to help provide low-resource populations with immediate access to the most effective HCV drugs on the market. The World Trade Organization 2001 Doha Declaration on the 1994 Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) allows governments flexibility in honoring the global rights of patent holders when public health is at stake. This measure gives governments bargaining power to negotiate price reductions with pharmaceutical companies, including the ability to enact compulsory licensing of on-patent drugs to allow local manufacture of generic versions without the consent of the patent holder. Governments can also import drugs from other countries that offer prices lower than domestic rates, encouraging competition (http://www.who.int/phi/phi_trips_policybrief_en.pdf). In 1997, South Africa paved the way for compulsory licensing through the Medicines and Related Substances Control Amendment Act, making antiretroviral treatment more affordable in the midst of the HIV/AIDS epidemic [44]. Brazil adopted a similar policy in 2007 with the compulsory licensing of efavirenz for non-commercial, free HIV treatment [45]. Brazil has also demonstrated governmental ability to refuse to issue patents to foreign drug companies in the interest of public health. In 1999, Brazil amended its patent law to allow its regulatory agencies to deny patents on medical products if they would impede citizens' universal access to medical drugs, which is protected as a constitutional right [45].

Pay for performance

Another piece of the payment puzzle may be a pay-for-performance model. Pharmaceutical companies including Johnson & Johnson, Merck, Pfizer, and Novartis already engage in performance-based pricing agreements in Europe and the USA for drugs that treat cancer, high cholesterol, asthma, and numerous other conditions. Through

these programs, drug manufacturers reimburse public and private insurers for the cost of drugs or pay for additional treatment if individuals do not meet pre-set clinical benchmarks after using their medications as prescribed [46]. Although countries with a single payer system may have more leverage to negotiate such arrangements, multiple payers in the USA are among the pioneers of these programs. For example, US insurance company Cigna negotiated with Merck in 2009 to pay reduced rates for diabetes drugs if individuals using them are unable to effectively control their blood sugar. In the same year, Proctor & Gamble and Sanofi-Aventis agreed to reimburse insurer Health Alliance for medical costs associated with fractures among those adhering to their osteoporosis medications [46].

For HCV, a performance-based pricing system could translate to reimbursements from drug manufacturers if those treated do not achieve SVR after 12 weeks, for example, or if they experience serious adverse events leading to treatment discontinuation. Alternatively, for difficult-to-treat subgroups such as those with cirrhosis or treatment-experienced individuals who may ultimately require add-on therapy with NS5A or protease inhibitors, insurers could negotiate a predetermined price per SVR rather than separate payments for each treatment regimen attempted in pursuit of a cure. For example, manufacturers of DAA regimens could pay the cost of add-on therapy for those who fail to reach SVR with all-oral treatment. A pay-per-SVR system could create further incentive to use the most effective drugs as first-line therapy rather than starting with suboptimal regimens that result in more treatment failures. A recent study by Solem *et al.* presented in 2013 at the 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy found that second- and third-line therapy for HIV/AIDS in the USA costs 24% and 41% more than first-line therapy, respectively, partly because of increasing complications after initial treatment failure. HCV treatment will present a similar dynamic, and SVR-based pricing could help reduce long-term medical costs, particularly for difficult-to-treat groups.

When to pay: health benefits and cost effectiveness of early treatment

As all-oral CHC drugs receive FDA approval, some payers may weigh disease severity in the equation when developing criteria for treatment coverage. Antiretroviral coverage for HIV/AIDS has been the subject of similar debates in the USA, resulting in many low-income, HIV-positive individuals who are ineligible for treatment coverage through Medicaid until their infection has progressed to a full AIDS diagnosis, which satisfies the Medicaid definition of disability status (Henry J. Kaiser Family Foundation, http://kff.org/hivaids/fact-sheet/medicaid-and-hivaids/). Some payers may similarly restrict HCV treatment coverage to those with advanced fibrosis or cirrhosis, with the assumption that the cost of all-oral treatment will decrease before individuals in early fibrosis stages start exhibiting symptoms, or that they will be covered by a different payer by the time they advance to later stages of disease and require treatment.

Although it can take HCV-infected individuals 20–30 years to develop serious health consequences, treating them as early as possible after diagnosis minimizes CHC-related morbidity and mortality [47]. It is well documented that early treatment for CHC is more likely to result in SVR and less likely to induce serious side effects compared to later treatment; with current standard-of-care regimens, SVR rates for non-cirrhotic individuals (72% for genotype 1, 80% for genotype 2 or 3) are much higher than among those treated after developing cirrhosis (42% for genotype 1, 43% for genotype 2 or 3) (Merck & Co., http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202258lbl.pdf; Vertex Pharmaceuticals, http://pi.vrtx.com/files/uspi_telaprevir.pdf) [7,48]. This trend holds true among clinical trial data for all-oral regimens as well, with individuals in early fibrosis stages achieving SVR more reliably than those with cirrhosis [16,49]. In addition, early treatment harnesses preventive potential by removing infected individuals from the pool of transmitters soon after infection, increasing the number of possible infections prevented and reducing associated costs.

Cost-effectiveness analyses have demonstrated that treating younger cohorts of HCV-infected individuals maximizes medical costs averted and quality-adjusted life years gained [31,47]. Treating early in the natural history of disease also supports the cost effectiveness of CDC recommendations for one-time universal screening among individuals born between 1945 and 1965, for whom CHC prevalence is especially high. Several analyses estimate that birth cohort-based screening has the potential to identify up to 75% more HCV infections in this age group compared to risk-based screening, depending on the percentage of the population that is tested [3,47]. However, the cost effectiveness of this screening strategy is especially sensitive to treatment uptake rates, requiring a certain threshold rate to generate sufficient cost savings and life expectancy gains to offset screening costs [41,47]. In a recent study, McEwan *et al.* demonstrated that birth cohort screening is most cost effective when HCV-infected individuals are treated immediately after diagnosis [47]. Therefore, treatment at early stages of disease can not only reduce CHC-related morbidity and increase life expectancy for those who are already diagnosed, but can also increase treatment uptake rates overall, thereby helping to maintain the cost effectiveness of birth cohort screening and ensuring that many other infected individuals have the opportunity to be identified for treatment and possible cure.

Pricing dynamics

Cost-effectiveness

The price of all-oral regimens will also play a role in the cost effectiveness of CDC birth cohort screening recommendations. Rein *et al.* found that the cost effectiveness of birth cohort screening is most sensitive to the cost of CHC treatment. In this study, the incremental cost-effectiveness ratio, or cost per quality-adjusted life year gained, nearly tripled when the cost of triple therapy for genotype 1 infections was increased by 50% in sensitivity analyses [3]. Thus, the ultimate pricing of all-oral drugs has the

potential to affect both the number of currently diagnosed individuals who can afford treatment and the cost effectiveness of screening recommendations that influence the number likely to be diagnosed in the future. High treatment costs that reduce the cost effectiveness of screening practices would certainly undermine eradication efforts going forward, but could also adversely affect drug manufacturers over time by influencing the intensity of efforts to identify treatment-eligible individuals.

Price projections

If a 12-week course of sofosbuvir requires 34 g of drug and if 1 kg costs approximately $40 000 to produce, the cost to manufacture one 34-g regimen would be approximately $1400, excluding the costs of formulation, encapsulation, and marketing. Assuming that Gilead's final all-oral regimen includes a second DAA at a similar price, the cost to the manufacturer would be $2800 per person treated. The $70,000+ projected market entry price for the first all-oral combinations [32] illustrates the wide gap between cost and price, which will only be reduced over time through competition and eventual patent expiration unless advocates can successfully negotiate with drug manufacturers to improve access in the short term.

HIV/AIDS relief programs provide a hopeful comparison. WHO estimates that, in part because of market competition and compulsory licensing, the price of the least expensive, WHO-recommended first-line antiretroviral agents has dropped from approximately $10 000 per treated person per year to $116 in the past decade in many countries (http://www.who.int/phi/phi_trips_policybrief_en.pdf). Similarly, the Clinton Health Access Initiative reported that its total HIV/AIDS per person treatment cost in 2011, including drugs and care, was approximately $200 in certain parts of Africa, primarily because of cost negotiations with manufacturers for generic antiretroviral agents. As of September 2012, PEPFAR has supported treatment for approximately 5.1 million HIV-infected individuals worldwide, now at a per-person per-year cost of $768, of which $292 was spent on antiretroviral drugs (http://www.pepfar.gov/documents/organization/188493.pdf and http://www.pepfar.gov/documents/organization/201387.pdf). The PEPFAR per-person antiretroviral drug costs represent only 2.3% of average per-person yearly expenditures by the Ryan White-funded ADAPs in the USA, which are themselves lower than market rates (National Alliance of State and Territorial AIDS Directors, http://nastad.org/docs/NASTAD-National-ADAP-Monitoring-Project-Report-Module-1-2013-1.pdf), providing evidence that price flexibility can be negotiated with drug manufacturers. To reach under-resourced communities, HCV drugs will need to meet similar price targets, both through market forces and commitments by drug companies for compassionate use.

Narrowing the access gap

Continued drug development

Achieving timely access to effective, affordable HCV drugs, particularly in regions with predominantly non-genotype 1 infections, will require additional strategies. The genotypes with the fewest therapeutic options to date affect tens of millions of people and should be the focus of continued drug development research. Specifically, genotype 4 is most prevalent in Egypt, where 15–20% of the population, approximately 12–16 million people, is infected with HCV [50,51]. Genotypes 5 and 6 are most common in South Africa and Southeast Asia, respectively [52].

High levels of genetic diversity among HCV genotypes and even within individuals, where quasispecies evolve spontaneously in response to the host immune system, pose challenges for pangenotypic drug development (http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/index4.html). However, universal drug combinations would decrease the cost of eradication efforts by eliminating the need for genotype testing and streamlining production and distribution processes.

Improved SVR rates for individuals with cirrhosis will also differentiate drug candidates in the future. To date, individuals with cirrhosis have comprised only a small percentage of the study population in most clinical trials testing all-oral regimens, and SVR rates for this group have been consistently lower than among those without cirrhosis. Because this subgroup is in greatest need of immediate treatment, drugs that can successfully cure them will play an important role in reducing the burden of disease towards eradication.

In addition, because of the teratogenic effects of ribavirin, treatment for pregnant women is another unmet need [53]. Approximately 4–7% of babies born to HCV-positive mothers acquire infection through vertical transmission, resulting in 7500 infected babies each year in the USA and even more in countries such as Egypt, where estimates of HCV prevalence among pregnant women are as high as 11% [53–55]. Further research is warranted to investigate the safety of all-oral regimens in pregnant women and children, as well as the ability of third-trimester HCV treatment to prevent perinatal transmission as it has for HIV [22,56,57].

Encouraging innovation

Governments in high-prevalence countries can be empowered to develop local research and manufacturing efforts for drugs and vaccines that, if successful, could be leveraged to drive the local economy through job creation and medical tourism from HCV-positive individuals living in nearby regions. Because some of these high-prevalence countries, such as Egypt, lack accredited infectious disease reference laboratories for viral load measurements, partnerships with global health organizations would increase the impact of such endeavors. Potential therapeutic targets for local research efforts could include natural products, as well as existing generics developed for other indications with potential cross-activity against HCV.

First-line eradication strategies

Optimizing screening and care

The opportunity for a cure for CHC without the side effects of interferon will be the driving force for increased treatment uptake among diagnosed individuals. For those unaware of their infection, a test, treat, and cure approach can increase diagnosis and uptake by combining enhanced screening practices with robust infrastructure facilitating linkage to care and follow-up.

In a cross-sectional study of HCV-positive individuals from the CDC National Health and Nutrition Examination Survey (NHANES) between 2001 and 2010, previous knowledge of HCV status was the only independent predictor of treatment uptake. In this study, 82% of those who sought and accepted treatment for HCV reported being aware of their infection prior to the NHANES test, compared to only 43% of those who were not treated. Furthermore, those who were unaware of their infection before they were screened through NHANES had lower income, less education, greater likelihood of excessive alcohol consumption, and lower likelihood of having health insurance compared to those who had been previously diagnosed. These results highlight the importance of aggressive screening efforts, particularly in populations less able to seek testing for HCV independently [58].

The 2010 World Hepatitis Alliance/WHO study estimated that nearly two-thirds of the world population lives in countries where HCV screening is not widely accessible (http://www.who.int/immunization/topics/hepatitis_b_survey_2010/en/). Although 59% of participating countries reported a designated pathway for screening, diagnosis, referral, and treatment (76%, 60%, and 33% in high-, middle-, and low-income countries; 40% in Africa; 70% in the Western Pacific region), most countries had few strategies in place for follow-up or retention. Encouragingly, 91% expressed interest in learning from best practices in other countries and in receiving assistance from WHO to improve surveillance and treatment access, evaluate existing interventions, develop prevention goals, and raise public awareness and reduce stigma associated with hepatitis. The Eurasian Harm Reduction Network reported that this 2010 study by WHO has already served as a stimulus for governments in Eastern Europe and Central Asia to begin to prioritize HCV awareness, testing, and treatment (http://www.idhdp.com/media/33100/ehrn_hepatitis_c_treatment_access_in_eeca.pdf).

International public health organizations can play an influential role in championing and implementing these efforts, and small NGOs can set the example in developing creative grassroots treatment strategies. For example, Médecins Sans Frontières (Doctors Without Borders) has developed an HIV treatment management model that empowers infected individuals living near one another to manage their care collaboratively by rotating responsibilities for drug pick-up at remote clinics and training them to monitor treatment adherence at the community level (http://www.msf.org/article/empowering-hiv-patients-manage-their-care). Another successful program, the UK-based One to One Children's Fund, connects 'expert patients' in 16 sub-Saharan countries with children who are HIV-positive to help them learn to live healthy lives with HIV. Each expert patient counsels up to 100 other patients per year, helping them adhere to their medications. These efforts actively combat the challenges brought about by resource and medical staff shortages, isolated clinics, and inadequate government support for HIV treatment infrastructure (http://www.onetoonechildrensfund.org/expert_patients and http://www.youtube.com/watch?v=bh6ETxl_0YI). With access to the most effective HCV drugs, similar strategies could boost treatment uptake and adherence, as well as prevention education, among high-risk groups. In fact, research in injection drug user populations has demonstrated that a community/peer support approach improves treatment adherence and reduces continued risk behavior for HCV [59].

Targeting high-risk groups and reinfected individuals

Targeting high-risk, high-prevalence populations for prevention, screening, and treatment can maximize the initial impact on the CHC disease burden. For example, an estimated 67% of injection drug users worldwide are HCV-positive, accounting for 60% of existing infections and 80% of new infections in developed countries [60,61]. Treatment uptake rates have historically been low in these populations, partly because of the risk of post-SVR reinfection through continued drug use [62–64]. Similarly, reinfection remains a concern among men who have sex with men (MSM), who can be re-exposed to HCV through high-risk sexual behaviors after SVR [64,65]. Accounting for the reality of reinfection and concerns about treatment adherence, numerous models of infection dynamics among injection drug users have demonstrated that antiviral therapy can successfully reduce CHC prevalence in these populations if treatment uptake levels are sufficient. Expected increases in uptake with all-oral DAA regimens can help these projections become a reality if access to drugs can be secured [64,66,67]. Similar targeted screening and treatment strategies can be deployed among other very high-risk groups, including prison populations in the USA, where HCV prevalence is estimated at between 12% and 35% [68].

Once effective vaccines against HCV are developed, they can be used to prevent post-treatment reinfection in high-risk individuals. In addition, clinical trials can determine whether long-term, low-dose antiviral therapy can prevent reinfection despite continued risk behavior. Until then, reinfection will remain a concern and payers will be expected to cover the cost of retreatment, even multiple times if necessary. For eradication to be successful, payers and other stakeholders will need to commit to the goal of curing all who are infected, regardless of how they became so. From a practical standpoint, individuals reinfected due to high-risk behaviors are also at highest risk of transmitting HCV to others; retreatment will not only benefit those who are reinfected, but will also contribute to overall cost containment and eradication goals by preventing further transmission.

Improving distribution of knowledge and drugs

In tandem with improved screening, treatment, and prevention strategies, deployment of the curative drugs themselves can be improved through unconventional partnerships with commercial leaders that have expertise in product distribution. The near-universal recognition of brands including Apple, Coca-Cola, McDonald's, Microsoft, Samsung, and Sony illustrates the logistical possibility of global market penetration and product distribution, even to very remote areas. Applying best practices from these successful industries can help in achieving worldwide access to a cure for HCV. For example, partnering with companies to place educational advertisements on the sides of vending machines could be a useful vehicle to

promote knowledge of HCV prevention and the availability of testing and curative treatment in settings as diverse as urban offices and community gathering places in rural areas.

Although these strategies will require significant investment of resources, several characteristics of all-oral drugs will reduce costs long-term. Eliminating interferon from treatment regimens will enable many primary care physicians to treat CHC, and fewer individuals will be lost to follow-up between physician diagnosis and referral to a specialist. In addition, the short treatment duration of all-oral regimens (8–12 weeks), the low incidence of adverse events to date, and the lack of drug resistance associated with certain DAA combinations will eliminate many treatment-related costs and improve uptake and adherence. Together, steps to identify populations at greatest risk, to optimize each step in the treatment cascade, to partner with public and private stakeholders, and to spur innovative research can contribute to cost savings and increase the number of HCV-positive individuals who can ultimately be treated and cured.

Concluding remarks

The availability of curative drugs for HCV engenders the ethical necessity to deploy treatment in pursuit of global eradication and an HCV-free generation. All-oral therapies soon to reach the market can cure only those who have access to them, perpetuating the disproportionately heavy burden of disease borne by economically marginalized groups and delaying access in developing countries. Increasing HCV diagnoses through enhanced public education initiatives, surveillance, and screening addresses only half of the equation; for diagnosis to equal cure, drug manufacturers, governments, NGOs, and private stakeholders will need to implement creative strategies to improve financial access and reach difficult-to-treat populations, while anticipating and mitigating potential unintended consequences of population screening and treatment programs. Leaders in all of these sectors hold the power to write a new chapter in the history of global disease eradication.

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