Hepatitis C Virus Therapeutic Development: In Pursuit of "Perfectovir"

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The next decade will be a crucial period in the public health response to hepatitis C virus (HCV) infection. The rapid development of direct-acting antiviral (DAA) therapy for HCV infection has brought considerable optimism to the HCV sector, with the realistic hope that therapeutic intervention will soon provide near-optimal efficacy with well-tolerated short-duration, all-oral regimens. As the zenith in HCV therapeutic development approaches, there remain several key obstacles to the broad implementation of interferon-free DAA regimens. The extent of HCV screening and disease assessment, global and national public health prioritization, and drug pricing will determine the potential impact on disease burden derived from introduction of these exciting new HCV therapies. Public health partnerships and advocacy will be crucial to remove barriers to enhanced HCV treatment access.

Keywords. hepatitis C; directly acting antivirals; global access.

Chronic hepatitis C virus (HCV) treatment has been interferon-based for the last 2 decades, with the addition of ribavirin (RBV) [1], pegylated interferon (peg-IFN) [2], and initial protease inhibitor direct-acting antiviral (DAA) therapies (telaprevir, boceprevir) [3, 4] providing stepwise improvements in the rate of sustained virologic response (SVR, equivalent to cure of infection) (Figure 1). Despite these improvements in interferon-containing regimens, treatment uptake has remained low in most countries, ranging from <1% to a maximum of 5% of people with chronic HCV initiating therapy each year [5]. Multiple factors have contributed to low HCV treatment rates, including suboptimal efficacy, medical comorbidities and therapeutic toxicity, prolonged duration of therapy (24–48 weeks), lack of awareness of the curative potential of treatment, lack of treatment infrastructure, limits on treatment reimbursement, social marginalization of many people with chronic HCV, and low rates of HCV screening and disease assessment [6–8]. Lower HCV treatment response rates in advanced liver disease have also limited the impact on disease burden [9].

Fortunately, recent years have seen a revolution in HCV therapeutic development, with the advent of DAA therapy and the move toward interferon-free regimens [10]. Within a few years, simple (single daily dosing oral regimens), highly tolerable, short-duration (6–12 weeks) therapy with extremely high efficacy (cure rates >90%) should be the norm. The broad implementation of such therapeutic regimens has the potential to produce one of the major turnarounds in disease burden seen in public health and clinical medicine.

This review will cover major recent developments in DAA therapy for chronic HCV and present challenges that need to be overcome to enable broad implementation of highly effective DAA regimens.

HCV LIFE CYCLE AND DAA THERAPY CLASSES

As the HCV viral life cycle has been more fully elucidated (Figure 2) [11], rational drug design and screening of large compound libraries have been used to identify

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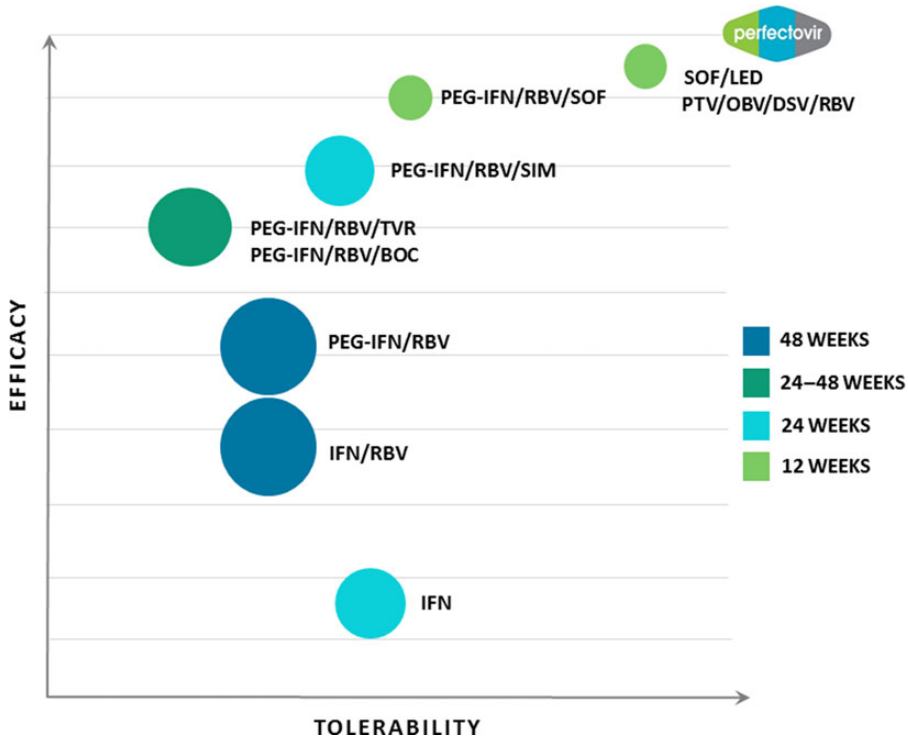

Figure 1. Advances in hepatitis C therapy with respect to tolerability and efficacy. Abbreviations: BOC, boceprevir; DSV, dasabuvir; IFN, interferon; LED, ledipasvir; OBV, ombitasvir; PEG-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; TVR, telaprevir.

small molecule inhibitors of various HCV proteins involved in HCV replication, the most important of which include (1) NS3/4A protease, which is involved in posttranslation processing of HCV polyproteins and also impairs the production of endogenous interferon by infected cells; (2) NS5B RNA-dependent RNA polymerase, which is required for copying the HCV RNA genome; and (3) NS5A protein, which is involved in forming the replication complex and possibly in viral assembly.

Employing drug development strategies similar to those used for human immunodeficiency virus (HIV) antiretroviral therapy, numerous inhibitors of these 3 viral targets are in clinical development, with initial DAA therapy licensure in 2011 of telaprevir and boceprevir (protease inhibitors combined with peg-IFN/RBV for chronic HCV genotype 1), followed in 2013 by simeprevir (protease inhibitor combined with peg-IFN/RBV for chronic HCV genotype 1) and sofosbuvir (nucleotide analogue combined with peg-IFN/RBV for chronic HCV genotypes 1, 4, 5, and 6 and with RBV for chronic HCV genotypes 1, 2, and 3). The rapid pace of therapeutic development is highlighted by the probable withdrawal of both telaprevir and boceprevir in the United States and Europe in 2015, due to availability of alternative agents.

The licensure of sofosbuvir and RBV combination provided the first interferon-free regimen (predominantly utilized as a 12-week regimen for genotype 2 and 24-week regimen for genotype 3), and a window into the future of chronic HCV treatment. The separate licensure of sofosbuvir and simeprevir-based regimens and the availability of phase 2 trial data demonstrating SVR rates of 92%–94% with a 12-week regimen of sofosbuvir plus simeprevir (with or without RBV) [12] also provided US-based clinicians the opportunity to create the first highly effective interferon-free regimen for chronic HCV genotype 1, albeit "off-label." Again based on favorable phase 2 trial data (SVR 98% for genotype 1, 92% for genotype 2, and 89% for genotype 3) [13], and following the licensure of the individual agents, the off-label combination of sofosbuvir plus daclatasvir (nucleotide analogue/NS5A inhibitor) for 12 (genotype 1) or 24 weeks (genotype 2/3) is being used in Europe and some non-European countries for treatment-naive and -experienced patients.

RECENT DAA DEVELOPMENTS

During 2014, major milestones were reached in the clinical development of DAA therapy for chronic HCV. Findings from phase 3 trials in treatment-naive and treatment-experienced patient populations with genotype 1 were reported for 2 interferon-free DAA regimens. The highly anticipated presentation of

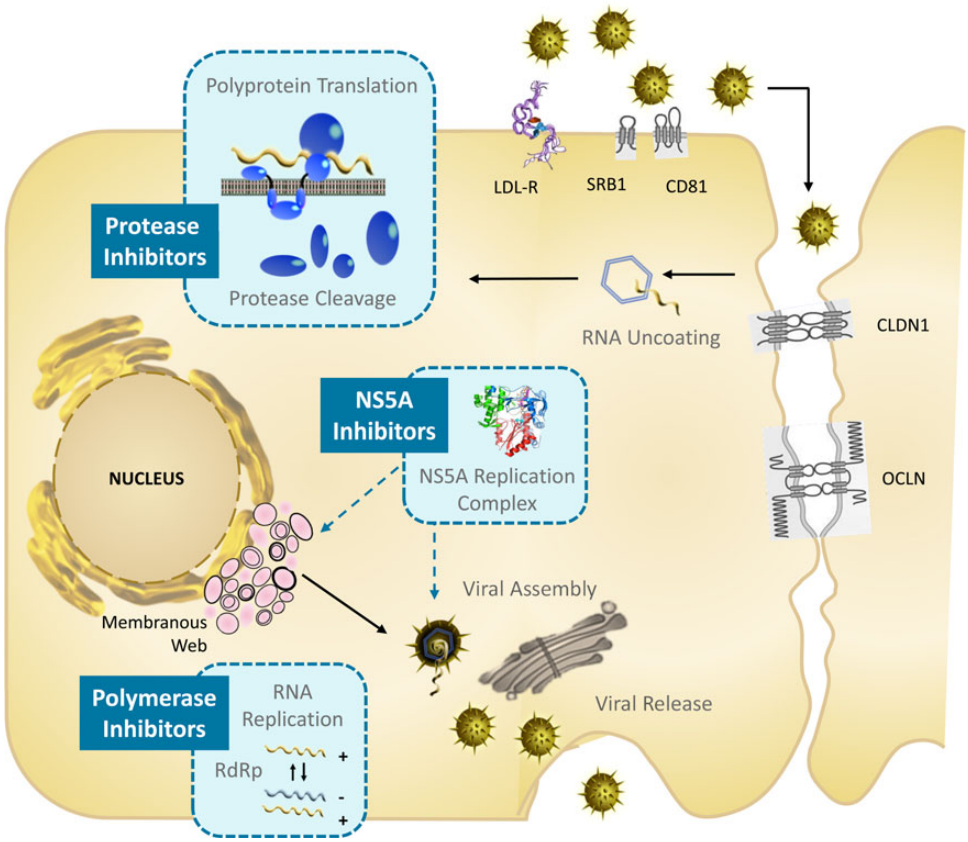

Figure 2. Hepatitis C virus (HCV) life cycle. Upon attaching to a sequence of entry factors, the virus enters the cell via clathrin-mediated endocytosis. After uncoating, the HCV RNA is translated using the internal ribosomal entry site inserting into host ribosomes to yield the HCV polyprotein, which is in turn cleaved by host and viral proteases to release the individual structural and nonstructural viral proteins. The replicase complex including the NS3 protease, NS5A, and the RNA-dependent RNA polymerase (RdRp) is assembled on lipid droplets in the membranous web adjacent to the cell nucleus. The positive strand RNA template is replicated to its negative strand and back to a positive-strand RNA, which is then packaged and released as a mature virion. Currently available direct-acting antivirals target the NS3 protease to prevent cleavage of the polyprotein, the NS5A protein, which serves as a scaffold for the replicase complex and is involved in viral assembly and the RdRp either as nucleotide analogues leading to chain termination or as nonnucleotide inhibitors through interaction with other regions of the polymerase protein. Although other life cycle events could be targeted, the potency of current agents, particularly when used in combination, will likely make this unnecessary.

these groundbreaking antiviral therapy trials at the International Liver Congress 2014 in London (ILC2014) was akin to the presentation of combination antiretroviral therapy trials at the World AIDS Conference 1996 (Vancouver). Multiple presentations at ILC2014 (and concurrent publications in the *New England Journal of Medicine*) on the combinations of sofosbuvir/ledipasvir (nucleotide analogue/NS5A inhibitor) [14, 15] from Gilead and ritonavir-boosted paritaprevir/ombitasvir/dasabavir (protease inhibitor/NS5A inhibitor/nonnucleoside polymerase inhibitor) [16–18] from AbbVie provided therapeutic development milestones, with major findings including:

- SVR rates consistently >90% in treatment-naive and treatment-experienced HCV genotype 1 populations;
- Treatment duration of 12 weeks sufficient for the majority of patients, with 8 weeks' duration for treatment-naive patients without cirrhosis treated with sofosbuvir/ledipasvir demonstrating similar efficacy to 12 weeks (SVR: 94% vs 96%);
- Lack of requirement for RBV addition to coformulated sofosbuvir/ledipasvir, enabling the first potential 1-tablet once-daily therapeutic regimen;
- Requirement for RBV addition to paritaprevir/ombitasvir/dasabavir for enhanced response in patients with HCV genotype 1a (SVR: 97% vs 90%), but not precirrhosis HCV genotype 1b (SVR: 99% vs 99%); RBV is also recommended for HCV genotype 1b patients with cirrhosis;
- Highly curative outcomes with a 12-week regimen of paritaprevir/ombitasvir/dasabavir/RBV in patients with cirrhosis (SVR: 92%) within a large randomized study of patients with cirrhosis, and similarly high SVR rates in subpopulations of patients with cirrhosis in sofosbuvir/ledipasvir trials;

- Limited baseline predictors of HCV response, given extremely high SVR rates, although genotype 1a patients with cirrhosis and prior null response to peg-IFN/RBV had SVR rates <90% and may benefit from extension of therapy to 24 weeks;
- Extremely high treatment completion rates, with well-tolerated regimens even with RBV inclusion.
- Extremely low rates of HCV resistance, including no sofosbuvir resistance recorded in phase 3 trials of sofosbuvir/ledipasvir.

The recent licensure of sofosbuvir/ledipasvir (8–24 weeks for genotype 1) and ritonavir-boosted paritaprevir/ombitasvir/dasabavir/RBV (12–24 weeks for genotype 1, without RBV for precirrhosis genotype 1b) adds to the current US and European licensed interferon-free regimen of sofosbuvir plus RBV (12 weeks for genotype 2, 24 weeks for genotype 1/3). Sofosbuvir plus simeprevir (12–24 weeks for genotype 1) has also been recently licensed following a period of off-label use, while off-label sofosbuvir plus daclatasvir (12 weeks for genotype 1, 24 weeks for genotype 2/3) is a commonly used regimen in Europe.

REMAINING REQUIREMENTS IN HCV THERAPEUTIC DEVELOPMENT

The bar has clearly been raised during 2014 in terms of the optimal regimen for HCV treatment ("perfectovir"). Ideally, such a regimen would have the following key attributes:

- Extremely high treatment efficacy (>95%);
- Pangenotypic activity (ie, similar dosing and duration across genotypes);
- Maintenance of high efficacy in decompensated cirrhosis and peritransplant settings;
- Minimal toxicity;
- Minimal HCV resistance;
- Ease of dosing, preferably 1 tablet once daily;
- Limited drug–drug interactions;
- Short duration;
- Affordability.

The presentation at ILC2014 of phase 2 trial data on the sofosbuvir/GS-5816 regimen (nucleotide analogue/NS5A inhibitor) from Gilead was an important step toward "perfectovir," given SVR rates >90% for HCV genotypes 1, 2, 3, 4, and 6, with a 12-week coformulated 1-tablet once-daily regimen [19]. Several other potential pangenotypic regimens are in development (Table 1). Thus, there is considerable optimism that "perfectovir" (or multiples thereof) will be a reality.

Shortening Treatment Duration

The journey from 48-week poorly tolerated interferon-based therapy to 8- to 12-week well-tolerated interferon-free therapy for chronic HCV genotype 1 has been rapid and remarkable. Initial modeling of interferon-free DAA therapy suggested that 8 weeks may be the treatment duration ceiling (or floor). However, the phase 2 National Institute of Allergy and Infectious Diseases Synergy Study that combined sofosbuvir/ledipasvir with either a protease inhibitor (GS-9451) or nonnucleoside polymerase inhibitor (GS-9669) demonstrated proof of concept that 6 weeks of triple DAA therapy could provide high efficacy for chronic HCV genotype 1 (>95% SVR was achieved in small study populations) [20].

The potency of DAA agents licensed and in development across several classes, and the level of pharmaceutical industry competitiveness, has led to ambitious targets with respect to treatment duration. Phase 2b studies are under way exploring 4- to 8-week strategies, generally with triple-DAA interferon-free regimens (Table 1).

CHALLENGES FOR GLOBAL HCV TREATMENT ACCESS

Enhanced HCV treatment efficacy, even with SVR rates consistently >90%, will have relatively limited impact on global HCV disease burden under current treatment rates [21]. In countries with the highest diagnosis and treatment rates, <5% of infected individuals are treated every year [5]. In many high-prevalence countries, <1% are treated annually [5]. The rising burden of advanced liver disease, including hepatocellular carcinoma (HCC), will continue in most settings unless both HCV treatment outcomes and uptake are improved [5, 22]. The simplified treatment delivery and reduced toxicity of interferon-free DAA regimens provides the foundation for enhanced HCV treatment uptake; however, there are many challenges in high-income and low- and middle-income country (LMIC) settings (Table 2).

High-Income Countries

A further crucial requirement toward "perfectovir" is the development of HCV treatment regimens that are affordable for healthcare systems in all settings, and provide a return on investment for the pharmaceutical industry, an essential driver of ongoing therapeutic development. US pricing of sofosbuvir (US$84 000 for 12 weeks) and simeprevir (US$66 000 for 12 weeks) following US Food and Drug Administration licensure in late 2013 provided a high threshold for HCV treatment in high-income countries, particularly given the subsequent off-label use of sofosbuvir plus simeprevir. Recent HCV drug pricing has generated significant controversy, leading to widespread media coverage and restrictions on access to new therapies by third-party and governmental payers. Although these highly effective DAA regimens are cost-effective by standard public health intervention criteria (less than US$50 000 per quality-adjusted life-year saved is generally used), the greatly enhanced

Table 1. Interferon-Free Direct Acting Antiviral Regimens for Chronic Hepatitis C Virus Genotype 1

Company	Protease Inhibitor	Polymerase Inhibitor: Nucleotide Analogue	Polymerase Inhibitor: Nonnucleoside Analogue	NS5A Inhibitor	Other	Duration	Total Tablets/ Dosing	Phase
Gilead		Sofosbuvir		Ledipasvir		8–24 wk[a]	1/daily	Licensed
AbbVie	Paritaprevir/ritonavir		Dasabuvir	Ombitasvir	± Ribavirin[b]	12–24 wk[c]	4–8[d]/bid	Licensed
BMS	Asunaprevir		Beclabuvir	Daclatasvir	± Ribavirin[e]	12 wk	2–8[d]/bid	3
Merck	Grazoprevir			Elbasvir		12 wk	1/daily	3
BMS[f]		Sofosbuvir		Daclatasvir		12 wk	2/daily	3
Gilead[f]		Sofosbuvir		GS-5816		12 wk	1/daily	3
Merck[f]	Grazoprevir	Sofosbuvir		Elbasvir		4–12 wk	2/daily	2
BMS	Asunaprevir	Sofosbuvir	Beclabuvir	Daclatasvir		4–6 wk	3/bid	2
AbbVie[f]	ABT-493			ABT-530	± Ribavirin	8–12 wk	2–4/daily-bid	2
Gilead[f]	GS-9857	Sofosbuvir		GS-5816		6–8 wk	2/daily	2
Merck[f]	Grazoprevir	MK-3682		Elbasvir or MK-8408		6–8 wk	2–3/daily	2

Abbreviations: bid, twice daily; BMS, Bristol–Myers Squibb.

[a] Eight weeks recommended for treatment-naive patients with genotype 1, Metavir F0–F3, and hepatitis C virus RNA level <6 million IU/mL; 24 weeks recommended for treatment-experienced patients with genotype 1 and cirrhosis.

[b] Ribavirin (RBV) used for all patients with genotype 1a and patients with 1b patients and cirrhosis.

[c] Twenty-four weeks recommended for treatment-experienced patients with genotype 1a and cirrhosis.

[d] RBV 400 mg and 600 mg tablets should be used once licensed, reducing total tablets per day to 4.

[e] RBV only evaluated in patients with cirrhosis.

[f] Also under evaluation as pangenotypic regimens.

potential demand of interferon-free regimens has raised concerns regarding their impact on healthcare budgets.

Antiviral therapy for hepatitis B virus and HIV generally requires several years to decades of ongoing therapeutic investment to optimize health benefits. However, the health benefits that can be achieved through short-duration curative HCV therapy leads to extremely high per-pill cost. HCV therapy cost-effectiveness is largely driven by prevention of downstream costs, in particular complications of advanced liver disease (decompensated cirrhosis, HCC), but these costs are incurred over decades rather than years.

Under current drug pricing models in high-income countries, treating all people with chronic HCV, even without increased screening and diagnosis rates, would have a major

Table 2. Strategies to Enhance Access to Interferon-Free Direct-Acting Antiviral Therapy

Strategic Area	High-Income Countries	Low- and Middle-Income Countries
Drug pricing	Discounting for large-scale payers; amortization (costs spread over several years rather than upfront); pharmaceutical industry competition.	Pharmaceutical and generic company agreements with voluntary licenses; individual country compulsory licenses with generic production.
Screening and diagnosis	Public awareness campaigns; birth cohort screening; antenatal screening; subsidized or free HCV testing; integration of HCV screening within harm reduction and addiction medicine services; prison entry screening.	Public awareness campaigns; blood donor screening; antenatal screening; linkage to HIV voluntary testing initiatives; prison entry screening.
Clinical assessment	Primary care practitioner education; HCV testing algorithms incorporating automatic HCV RNA testing of antibody-positive individuals; enhanced access to noninvasive methods of fibrosis staging.	Simplified and low-cost tools for detection of chronic HCV, such as antigen assays; low-cost methods of disease staging, such as APRI score.
Strategy development and public health advocacy	National HCV strategy development; HCV testing and monitoring policies; treatment guidelines; World Hepatitis Day activities; partnerships with civil society.	WHO HCV screening, treatment, and care guidelines, including regular revision; national HCV strategy development; World Hepatitis Day activities; partnerships with civil society.

Abbreviations: APRI, AST to Platelet Ratio Index; HCV, hepatitis C virus; HIV, human immunodeficiency virus; WHO, World Health Organization.

impact on healthcare budgets. Thus, alternative drug pricing strategies need be considered. The simplest and most commonly adopted policy is restriction to those with more advanced liver disease. Although disease stage–based restrictions may optimize benefits (cost-effectiveness) of therapy, potential downsides include losing patients to follow-up, reduced efficacy in advanced fibrosis (albeit largely overcome with interferon-free DAA regimens), lack of prevention of extrahepatic HCV manifestations, and lack of potential quality of life improvement among patients with early liver disease. Of great concern are recent restrictions on access to sofosbuvir in many areas of the United States based not on disease stage, but lifestyle issues such as ongoing alcohol and illicit drug use.

One strategy to address drug pricing would be to amortize the cost of therapy. For payers, the biggest challenge of HCV treatment is the enormous upfront cost. If treatment could be paid for over a period of 5 or even 10 years, the immediate budget impact would be dramatically reduced. For current market leaders, signing people up for therapy now, even with deferred payment, ensures they maximize sales before new competition enters the market.

Although important, drug pricing is only one aspect of optimizing the potential impact of new HCV therapies. There are several key points along the HCV clinical pathway where specific strategies are required. First, and foremost, low rates of screening and diagnosis in many countries [5] need to be addressed. In most high-income countries, <50% of HCV-infected individuals have been diagnosed. Increasing screening rates requires active HCV public policy, ideally with development of a national strategy to address HCV. The recent upgrading of HCV screening within US public health priority, enabling subsidized testing, is a crucial step. Birth cohort screening in the United States [23], and consideration of similar policies in other countries [24], should lift the proportion of the HCV-infected population diagnosed.

Second, enhanced assessment of infection and disease stage are required. Many patients receive a diagnosis of "hepatitis C" without confirmation of chronic HCV by HCV RNA evaluation. In those with chronic HCV, liver disease staging assessment remains inadequate. As mentioned, a degree of patient prioritization for highly priced new HCV treatments may be required, with targeting of those with more advanced liver disease during the initial years of the interferon-free DAA era. In this interim period, chronic HCV should continue to be treated primarily as a chronic liver disease with enhanced capacity for staging of fibrosis. Noninvasive methods of liver disease staging, including hepatic elastography (FibroScan), will be central to this strategy. As lower-priced interferon-free DAA regimens become available, the strategy should switch to treatment of HCV as predominantly an infectious disease involving therapeutic intervention for all stages of disease. Patients with advanced liver disease will continue to require specific liver disease management.

Third, enhanced HCV treatment infrastructure, particularly beyond tertiary care, will need to be developed to facilitate broadened access. A range of models of HCV care have been developed and successfully evaluated in community and primary care [25, 26], opiate pharmacotherapy [27], and prison [28] settings. The era of interferon-free DAA therapy should provide even greater feasibility for expanded models of care.

Fourth, public health advocacy, including partnerships between affected communities, clinicians, academics, and government bodies, together with strategic action are required to advance HCV as a health priority. Development and implementation of national HCV strategies, accompanied by increased dedicated funding, are clear priorities. Even with lowering of drug pricing, the total investment in HCV therapy in most high-income countries will need to increase several-fold to stem the rising burden of HCV-related liver disease.

Low- and Middle-Income Countries

The burden of HCV infection and liver disease is considerable in many LMICs [29]. The HCV epidemic in Egypt has been well characterized, with extremely high population prevalence and escalating advanced liver disease burden [30]. Unlike HIV, where the majority of infections are in the African continent, the majority of people with chronic HCV reside in Asia, with the largest number in China and India [29]. HCV epidemics in LMICs have generally been driven by iatrogenic infections; however, injecting drug use is also now a major contributor in many countries [29].

The success of global HIV treatment initiatives provides the precedent for successful therapeutic intervention for management of a chronic viral infection. The number of people with chronic infection is larger for HCV (80–140 million) [31, 32] than HIV (35 million) [33]; however, one of the challenges for healthcare prioritization is the relatively poor data on HCV epidemiology from most countries. Despite larger numbers of people infected, slower HCV disease progression and the short duration and highly curative nature of interferon-free DAA therapy enhances the feasibility of replication of HIV successes. The global HIV treatment initiative has required more than a decade of concerted effort, including several key components critical to success:

- Involvement of affected communities in policy development;
- Public health advocacy, driven by partnerships between civil society, academia, healthcare professionals, funding bodies, and government;
- Drug price reform, particularly development of low-cost generic antiretroviral therapy;
- Establishment of the Global Fund for HIV/AIDS, Malaria and TB, with multi-billion-dollar annual investment from public and private funding bodies;
- Development of global and national HIV strategic plans;

- Strategic planning underpinned by HIV surveillance and mathematical modeling;
- Public health partnerships between prevention and treatment and care initiatives.

Although there are clear differences between HIV and HCV, and a need for the global HCV response to define its own territory and pathway, there are many lessons to be learned from the HIV response. Drawing on experiences in HIV, community HCV treatment activism and engagement with the pharmaceutical industry has commenced.

The recently announced partnership between Gilead and Indian generic companies to allow low-cost (1%–2% of the US listed price) generic production of sofosbuvir and sofosbuvir/ledipasvir under voluntary licenses for 90 LMICs, and the Gilead–Egyptian government agreement on supply of low-cost sofosbuvir ($300 per month) are positive developments toward enhanced global HCV treatment access. The estimated relatively low production costs of most DAA agents [34] provides further confidence that low-cost generic drug supply will be feasible for other combination DAA regimens.

Other strategies that may be utilized on the path toward global HCV treatment access are compulsory licences to allow production or importation of generic drugs. Brazil and Thailand are countries that have issued compulsory licenses for supply of antiretroviral therapies.

Leadership from key international organizations will be crucial to expanded HCV treatment access. The World Health Organization released in 2014 its first "Guidelines for the Screening, Care and Treatment of Persons with Hepatitis C Infection." These guidelines focus on HCV clinical management in LMICs and provide a framework for leveraging enhanced country-level action. However, public health investment in HCV at national and global levels remains frighteningly inadequate.

As in high-income countries, drug pricing will be crucial; however, major investment in HCV treatment infrastructure and greatly enhanced efforts at key points along the HCV clinical pathway will be required to improve HCV treatment access. The need to improve HCV screening is underpinned by even lower screening rates in LMICs than in high-income countries [5]. Simplified HCV assessment and treatment monitoring tools are required, with development of low-cost HCV RNA tests and evaluation of HCV antigen assays.

Global HCV treatment access and impact will require considerably more than the development of "perfectovir," although the recent exciting advances in HCV therapeutic development provide optimism and should empower the HCV sector to move toward a new era of improved liver health for millions of people.

Notes

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