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Minimum Target Prices for Production of Direct-Acting Antivirals and Associated Diagnostics to Combat Hepatitis C Virus

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Combinations of direct-acting antivirals (DAAs) can cure hepatitis C virus (HCV) in the majority of treatment-naïve patients. Mass treatment programs to cure HCV in developing countries are only feasible if the costs of treatment and laboratory diagnostics are very low. This analysis aimed to estimate minimum costs of DAA treatment and associated diagnostic monitoring. Clinical trials of HCV DAAs were reviewed to identify combinations with consistently high rates of sustained virological response across hepatitis C genotypes. For each DAA, molecular structures, doses, treatment duration, and components of retrosynthesis were used to estimate costs of large-scale, generic production. Manufacturing costs per gram of DAA were based upon treating at least 5 million patients per year and a 40% margin for formulation. Costs of diagnostic support were estimated based on published minimum prices of genotyping, HCV antigen tests plus full blood count/clinical chemistry tests. Predicted minimum costs for 12-week courses of combination DAAs with the most consistent efficacy results were: US$122 per person for sofosbuvir+daclatasvir; US$152 for sofosbuvir+ribavirin; US$192 for sofosbuvir+ledipasvir; and US$115 for MK-8742+MK-5172. Diagnostic testing costs were estimated at US$90 for genotyping US$34 for two HCV antigen tests and US$22 for two full blood count/clinical chemistry tests. *Conclusions:* Minimum costs of treatment and diagnostics to cure hepatitis C virus infection were estimated at US$171-360 per person without genotyping or US$261-450 per person with genotyping. These cost estimates assume that existing large-scale treatment programs can be established. (HEPATOLOGY 2015;61:1174-1182)

Treatment scaleup for the estimated 150 million people infected with hepatitis C virus (HCV) remains an unresolved public health challenge, and up to 500,000 people die annually as a result of HCV-related liver complications.[1,2] For widespread treatment of HCV in low- and middle-income countries (LMICs) to be feasible, short-course antiviral treatments need to be available at very low costs. Several combinations of direct-acting antivirals (DAAs) have been recently licensed or are being developed that can cure HCV in the majority of treatment-naïve patients for a range of genotypes. These drugs generally have a good safety profile and rates of sustained virological response (SVR) close to 100%, including in traditionally difficult-to-treat patients. The promising clinical trial results for these DAAs suggest they will eventually replace current interferon (IFN)-based treatment.[3]

The U.S. launch prices for a 12-week course of the recently approved DAAs, sofosbuvir and simeprevir, are US$84,000 and US$66,000, respectively.[4] At these prices, treatment would be out of reach for the majority of those in need in LMICs, and these medications would need to be rationed in many high-income settings.[3] However, we have previously estimated that minimum production costs of sofosbuvir and simeprevir could be as low as US$68-136 and US$130-270, respectively,

Abbreviations: APIs, active pharmaceutical ingredients; ARVs, antiretrovirals; DAAs, direct-acting antivirals; FPP, finished pharmaceutical product; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; LMICs, low- and middle- income countries; LLOD, lower limit of detection; NS, nonstructural protein; PCR, polymerase chain reaction; SVR, sustained virological response; TRIPS, Trade-Related Aspects of Intellectual Property Rights.

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with economies of scale.[5] Achieving these low prices is necessary to facilitate treatment scaleup.

The ability to diagnose and monitor HCV simply and inexpensively will be important to ensure widespread access to HCV treatment. At present, because of the limited efficacy and poor tolerability profile of current treatments, HCV diagnosis and monitoring requires a range of complex tests before and during treatment, including genotyping, HCV-RNA quantification by polymerase chain reaction (PCR) assays, and FibroScan to evaluate severity of liver disease.[6] Most resource-limited settings are not equipped to undertake complex laboratory diagnostics at scale. Furthermore, with current treatments, regimen duration and rates of treatment success are highly dependent on the infecting genotype, which varies significantly in its relative prevalence worldwide.[7] Encouragingly, the improved side-effect profile and high SVR rates of new DAAs should allow for simplification of both diagnosis and monitoring of patients and may offer the potential for a standardized package of care of patients.[8]

DAAs for HCV infection have similar chemical structures and mechanisms of action to antiretrovirals (ARVs) used for the treatment of human immunodeficiency virus (HIV) infection. Generic ARVs are currently manufactured at a very low cost, covering treatment for over 10 million people in LMICs. ARV prices have fallen progressively through generic competition, economies of scale from more people treated, and improved efficiencies in procurement of raw materials and production processes for active pharmaceutical ingredients (APIs).[9,10] Recognizing the limited laboratory infrastructure in resource-limited settings, the public health approach to scaling up access to treatment for HIV has relied on a minimal use of laboratory investigations. In order to replicate the successes of providing widespread ARV therapy, the combined costs of HCV treatment and monitoring will need to be substantially lowered.

Using the cost of HIV drugs as a framework for analysis, we can make estimates for the potential cost of HCV DAAs.[3,5,11,12] This analysis aimed to estimate the minimum costs of DAA treatment considered most promising for large-scale treatment programs in LMICs and associated diagnostic monitoring.

Materials and Methods

Clinical trials of HCV DAAs were reviewed to identify combinations with phase II or III trial results, good safety profiles, high SVR rates, a future program of clinical trials in different genotypes, and the potential to reduce treatment duration. Three HCV DAAs—ledipasvir (phase III), MK-8742 (phase III), and MK-5172 (Phase III)—were prioritized for further evaluation based on this review. These DAAs were combined with results from three previously studied drugs: sofosbuvir, daclatasvir, and ribavirin.[5] Table 1 shows summary SVR rates for these combinations of DAAs, based on combining the results of all published trials available.

Based on the chemical synthesis and molecular structure, an approximate range of cost for the API of each DAA was estimated. These calculations assumed an API demand that would cover treatment for 5 million people. Treating 5 million people was considered the starting point for a volume demand large enough to reasonably minimize API prices while assuming cost pressures in the market through competition.

To determine the manufacturing cost, retrosynthetic analysis of each target DAA into its precursor structures and routes of chemical synthesis were taken from the available literature. Additional considerations in assessing the complexity of chemical synthesis included recognizing the cost-limiting intermediates, number of steps of synthesis, and availability/pricing of raw materials.[5]

From the manufacturing cost of an API, a 25% markup as a profit margin for sales with an add-on of 40% for conversion to the finished pharmaceutical product (FPP) was applied to estimate the overall predicted unit cost per person. Estimated API costs for the selected DAAs ranged from US$5,000-7,000 per kg. Because these APIs are relatively expensive at the assumed volume demand, a 40% markup was applied to estimate the cost of the finished dosage form. These assumptions are based on the method previously used to estimate minimum production costs of other DAAs.[5]

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Table 1. Results From Clinical Trials: Arms Combined, Treatment Naïve, by Genotype

Combination	Trial	Genotype	Treatment Arms	SVR Rate
Daclatasvir+sofosbuvir	AI444-040[13] Combined 24wk Arms*	1	12wk (n = 41)	95% (SVR-24)
			24wk (n = 29)	97% (SVR-24)
		2 and 3	24wk (n = 30)	93% (SVR-24)
Sofosbuvir+ribavirin	Combined QUANTUM[14] and ELECTRON[15,16]	1	12wk (n = 69)	75% (SVR-12)
	Combined POSITRON,[17] VALENCE,[18] FISSION,[19] and PHOTON-1[20]	2	12wk (n = 237)	94% (SVR-12)
	Combined POSITRON,[17] FISSION,[19] and PHOTON-1[20]	3	12wk (n = 323)	59% (SVR-12)
	Ruane et al.[21]	4	12wk (n = 14)	79% (SVR-12)
Sofosbuvir+ribavirin	Combined SPARE,[22] QUANTUM,[14] and PHOTON-1[20]	1	24wk (n = 168)	73% (SVR-12)
	VALENCE†[18]	3	24wk (n = 105)	93% (SVR-12)
	Ruane et al.[21]	4	24wk (n = 14)	100% (SVR-12)
Sofosbuvir/ledipasvir	Combined LONESTAR[23] and ION-3[24]	1	8wk (n = 235)	94% (SVR-12)
	Combined LONESTAR,[23] ION-1,[25] ION-3,[24] SYNERGY,[26] and ERADICATE[27]		12wk (n = 544)	95% (SVR-12)
	ION-1[25]		24wk (n = 217)	97% (SVR-12)
	ELECTRON-2[28] Cohort 1	3	12wk (n = 25)	64% (SVR-12)
MK-8742/MK-5172	C-WORTHY[29-31] Combined 12wk arms	1	12wk (n = 103)	95% (SVR 4-24)

*Combined arms of sofosbuvir × 7 days, then sofosbuvir+daclatasvir × 23 weeks + 24-week sofosbuvir+daclatasvir.

†Excluding 12-week regimen for genotype 3.

Abbreviations: wk, week; SVR-4, undetectable hepatitis C virus RNA 4 weeks after finished treatment; SVR-12, undetectable hepatitis C virus RNA 12 weeks after finished treatment; SVR-24, undetectable hepatitis C virus RNA 24 weeks after finished treatment.

Using the daily dose of each DAA identified from clinical trials, the total drug requirement for a 12-week regimen was calculated. With these calculated production costs per gram of DAA together with the total amount of drug required, a minimum cost estimate for a 12-week treatment course of each DAA was calculated. Using these costs and the mid-point estimates for ribavirin, daclatasvir, and sofosbuvir taken from a previous analysis,[5] the production costs of two-drug combination regimens could be estimated based on the combinations currently being studied in clinical trials (Table 1).

Each trial for the chosen DAA combination regimens was studied for treatment-related adverse events. Using the safety profiles from these clinical trials, the minimal necessary tests during treatment were proposed as two full blood count and two clinical chemistry tests, taken before the start of treatment and then at week 4 to monitor ongoing safety issues. Clinical chemistry tests taken before treatment could also be used for simple staging of liver disease (APRI/FIB4) to guide decisions on the duration of DAA treatment.

Using the current literature on the analytical performance characteristics of the available HCV diagnostic tests, it was determined that the lab-based HCV Architect antigen test could be a reasonable alternative in comparison to HCV-RNA PCR for detecting HCV RNA for diagnosis and post-treatment monitoring of HCV patients. In this proposed system, a single antigen test would be performed before the start of treatment to confirm active HCV infection, and then a second antigen test would be performed 6 months after the end of treatment, to confirm that reinfection or relapse had not occurred. Costs of diagnostic support were estimated based on published prices of tests from developing countries.[32,33]

Using these estimates and the calculated production costs of DAA combination regimens, an overall care package for HCV diagnosis, treatment, and monitoring was calculated.

Results

The DAAs, sofosbuvir, daclatasvir, ribavirin, ledipasvir, MK-8742, and MK-5172, were considered a priority for the cost analysis. Minimum costs of production of sofosbuvir, daclatasvir, and ribavirin were estimated in a previous analysis.[5] Figure 1 shows these HCV DAA structures as well as the route of synthesis and raw materials in production for ledipasvir, MK-8742, and MK-5172. A summary of the estimated cost per person for a 12-week course of each HCV DAA is shown in Table 2.[5]

MK-8742. MK-8742 is a tetracyclic indole-based nonstructural (NS)5A inhibitor with a molecular weight of 882 g/mol.[34] At a 50-mg/day dose, a 12-week course of treatment will require 4.2 g of API. Assuming 5 million patients would be treated, 21 metric tonnes of API would be required. The cost-limiting monobrominated imidazole intermediate (compound 5) and the efficiencies attributed to obtaining chirally pure API at a late stage in the synthesis add substantial expense to the five-step synthesis of MK-8742. The estimated manufacturing cost of MK-8742 FPP is US$10.50/g, based on a nominal API manufacturing cost of US$6,000/kg. At a daily dose of 50 mg, the

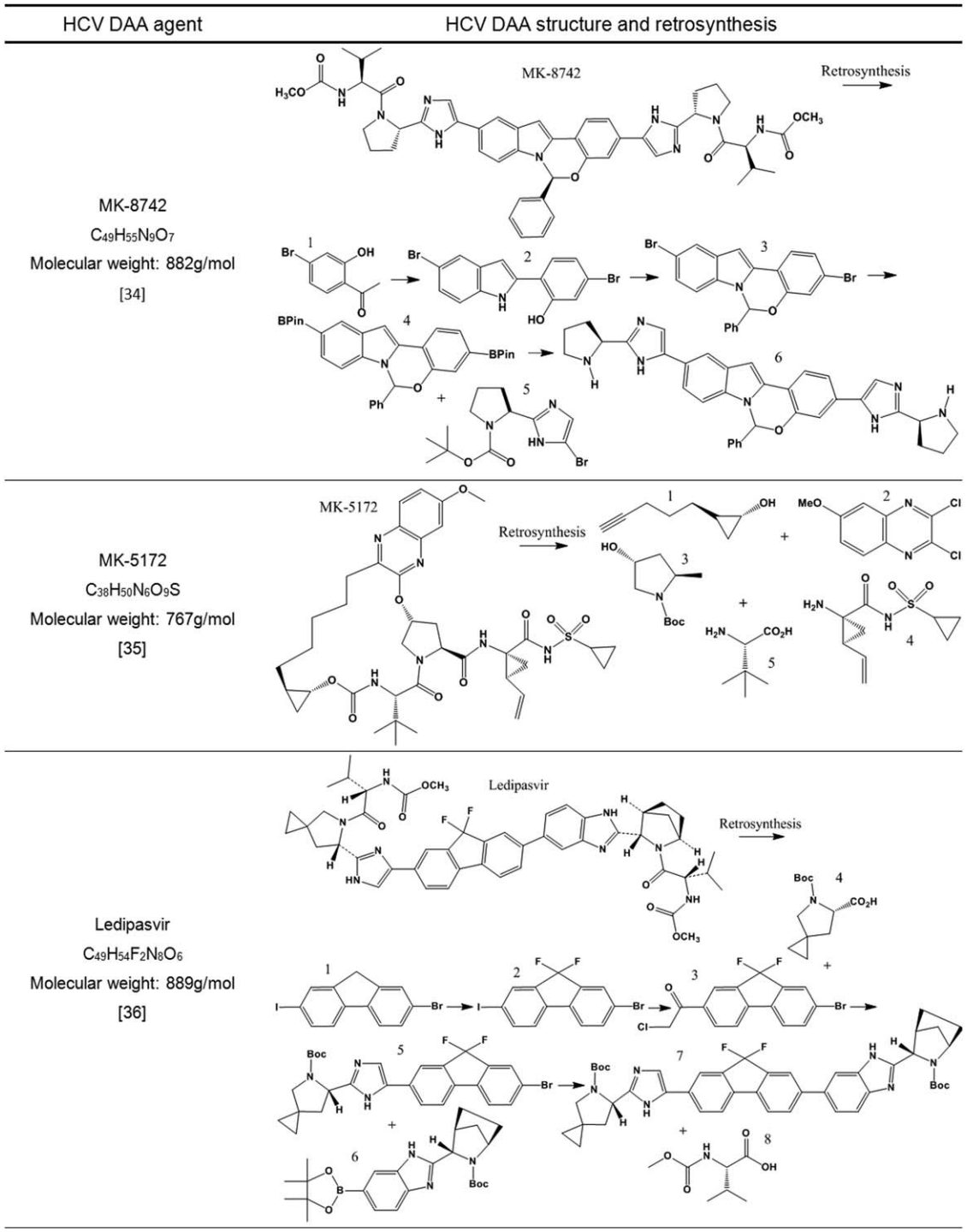

Fig. 1. HCV DAA structure and likely cost limiting materials in production.

estimated production cost for 12 weeks per person-treatment is thus estimated as US$44 per person.

MK-5172. MK-5172 is a macrocyclic NS3/4a protease inhibitor with a molecular weight of 767 g/mol and chemical formula of $C_{38}H_{50}N_6O_9S$.[35] At a daily dose of 100 mg, 12 weeks of treatment require 8.4 g of API. Assuming 5 million patients would be treated, 42 metric tonnes of API would be required. Compounds 2 and 3 are relatively easy to make, and compound 4 is commercially available and therefore cheap. The yields for the most difficult steps of the synthesis—forming the macrocyclicurethane-lactam—are highly efficient. Even though compound 4 is relatively expensive to make, it is incorporated in a high-yielding last step.[36] On 42 metric tonnes of volume demand, the API is estimated to cost US$5,000/kg.

Table 2. Predicted Minimum Costs of Selected HCV DAAs for 12 Weeks of Treatment

Agent	Patent Expiry	Daily Dose (mg)	Overall Dose Per 12-wk (g)	Estimated cost/g (US$)	Predicted Cost (US$)
Ribavirin	Generic	1,200	100.8	0.34*	$48
Daclatasvir	2027	60	5.0	4.00	$20
MK-8742	2028	50	4.2	10.50	$44
Sofosbuvir	2029	400	33.6	3.00	$101
MK-5172	2030	100	8.4	8.75	$74
Ledipasvir	2030	90	7.6	12.25	$93

*Current mid-point cost of API from 3 Chinese suppliers.[5]
Abbreviation: wk, week.

Accordingly, a 12-week treatment with MK-5172 has an estimated cost of US$74 per person.

Ledipasvir. Ledipasvir is a NS5A inhibitor with an unsymmetric benzimidazole-difluorofluorene-imidazole core.[37] At a daily dose of 90 mg, a 12-week course of ledipasvir requires 7.6 g of API. This results in an API demand of 38 metric tonnes to treat 5 million patients. Fluorene is the ultimate starting material for this synthesis, with a current price of US$4/kg. Intermediates 4 and 6 for the synthesis of the API are cost-limiting. Overall production costs for the FPP are estimated at US$12.25/g from an API cost of US$7,000/kg, giving an estimated cost per 12-week course of US$93 per person.

Combination Regimens. Using the calculated DAA drug prices, the estimated costs of the four most effective combination regimens are shown in Table 3. Previously published cost estimates for ribavirin, sofosbuvir, and daclatasvir[5] were combined with those of the three new DAAs. The 12-week combination of MK-8742 and MK-5172 has an estimated minimum cost of US$118 per person. A 12-week course of daclatasvir or ribavirin and sofosbuvir could cost US$121 or US$149 per person-treatment, respectively. A treatment course combining sofosbuvir and ledipasvir could cost US$129 for 8 week or US$193 for 12 weeks per person. For some patients or some regimens, a 24-week treatment might be necessary, doubling the estimated treatment costs from the 12-week regimen.

Diagnostic Testing. The favorable safety profile of these DAA combinations suggests that safety monitoring could be limited to two full blood count plus clinical chemistry tests, including alanine transaminase and creatinine, one pretreatment, and another during treatment.

Results from validation studies indicate a correlation between HCV viral load and antigen quantification, irrespective of HCV genotype, when HCV RNA is >2,000 IU/mL.[38,39] Compared with HCV RNA, the Architect antigen test was specific, user-friendly, and less expensive.[40,41] One limitation is the sensitivity,[42,43] which corresponds to a lower limit of detection (LLOD) of approximately 2,000-IU/mL HCV-RNA levels.[44,45] Given that the majority of HCV infections and relapsers are associated with a high level of viremia (>2,000 IU/mL),[33,43] the HCV antigen assay is a robust alternative to HCV-RNA PCR to confirm chronic infection.[42-44,46] The reduced sensitivity limits its clinical utility for use during therapy, but could prove to be useful in monitoring patients with virological relapse or reinfection.

Monitoring could involve an HCV antigen test pretreatment to establish infection and a repeat test 6 months after stopping treatment to ensure that reinfection or relapse has not occurred. If treatment is not pangenotypic, HCV genotyping could be added for pretreatment monitoring. Diagnostic testing costs were estimated at US$90 for genotyping, US$34 for two HCV antigen tests, and US$22 for two full blood count and clinical chemistry tests.[32,33]

Overall Costs. The minimum costs of treatment, diagnostic monitoring, and genotyping to cure HCV are shown in Fig. 2. Minimum costs per person range from US$174 for 12 weeks of MK-8742 and MK-5172 with no genotyping to US$444 for 24 weeks of sofosbuvir plus ribavirin with genotyping.

Discussion

This analysis suggests that a 12-week IFN-free regimen supported by minimal diagnostic testing could cost US$264-444 per person, if genotyping is required. The use of pangenotypic drugs with no genotyping could cost US$171-360 per person. Recognizing that specialist physician care and advanced laboratory monitoring is not feasible at the scale required to treat large numbers of patients in resource-limited settings, this simplified, easy-to-administer, and tolerable DAA treatment approach would enable HCV to be managed at lower-level health facilities, thereby facilitating widespread treatment access.[3]

Table 3. Predicted Costs of Key Drug Combinations

Regimen	Daily dose (mg)	Duration (Weeks)	Predicted Unit Cost (US$)
MK-8742+MK-5172	50+100	12	$118
Daclatasvir+sofosbuvir	60+400	12	$121
		24	$242
Sofosbuvir+ledipasvir	400+90	8	$129
		12	$193
Sofosbuvir+ribavirin	400+1,200	12	$149
		24	$298

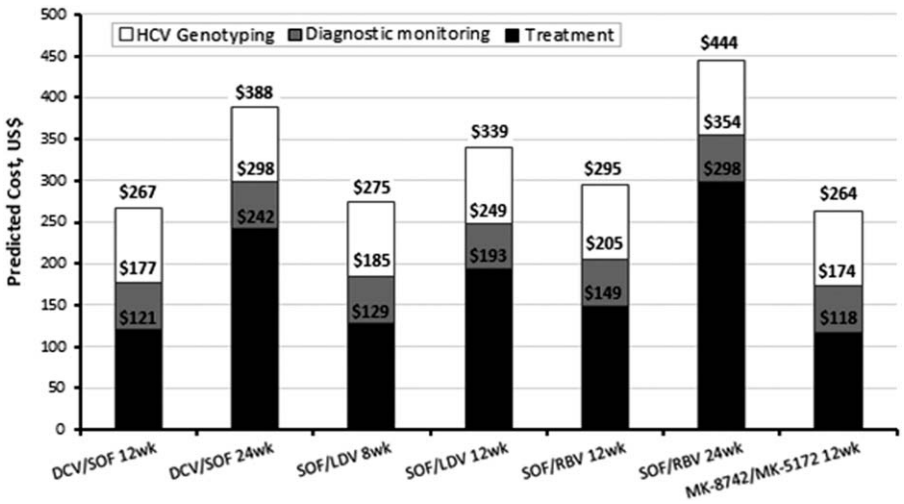

Fig. 2. Minimum costs of treatment, diagnostic monitoring, and genotyping. Abbreviations: DCV, daclatasvir; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir.

The cost of ARVs in LMICs is mainly driven by the price of the API, which constitutes 65%-90% of the total market price.[10,11] Through increased volume demand, cheaper raw materials, and improved chemical synthesis, the price of generic antiretroviral APIs has significantly fallen over the last decade. For example, generic manufacture of efavirenz API has fallen from US$1,100 to US$130/kg over this period.[10] This suggests that there is an opportunity for future price reductions for DAA APIs through these same mechanisms.[10,11] With this in mind, the estimates in this analysis are based on moderate volume demand (5 million people treated per year) and are thus dependent on sizeable procurement orders and the presence of competition in the market as one mechanism to encourage price reductions. There are a number of pricing and procurement mechanisms that need to be utilized in order to secure such orders, and this depends on commitment to improving access to treatment by a range of actors, including originator pharmaceutical companies, generic manufacturers, governments, and donors.

The DAA patent holders (originator companies) are likely to offer treatment to the poorest countries at a discounted price—this is already the case for sofosbuvir.[11] For other countries, the most commonly observed marketing strategies include voluntary licensing agreements to supply medicines to low-income countries, negotiating terms of tiered pricing for middle-income countries, and to maintain standard pricing for those countries considered high-income.[3]

However, these strategies are unlikely to stimulate the needed levels of access to those countries most heavily burdened. Patents for these DAAs do not expire until at least 2027, restricting generic production until this time.[47-50] In order to overcome patents and allow for generic drug production, governments have invoked the Trade-Related Aspects of Intellectual Property Rights (TRIPS) flexibilities to overcome patent barriers and allow generic competition for ARVs and other essential medicines.[3,12]

Generic competition has been central to the decreasing prices of HIV treatment and has mainly been facilitated by patent opposition in India.[51] Generic drugs are generally considerably cheaper than the originator versions and, furthermore, remain at a constantly low level for LMICs. Another option under the TRIPS flexibilities is employing stricter standards for patentability and opposing new applications.[52] The patent for sofosbuvir has received pregrant opposition on the basis of lack of innovation, which, if approved, will increase competition and help drive down the cost. Such approaches could be employed to increase generic access to other DAAs.

In addition to lowering drug costs, large-scale treatment programs for HIV only became feasible after significant support from international donors, including the establishment of new funding mechanisms. International donors continue to play a significant role in financing the supply of HIV medicines. Owing to the size of the potential orders, large donor organizations also have more bargaining power than individual countries, which will be pivotal in securing lower prices. While international funding for HCV programmes is needed, it is also essential that governments begin to allocate sustained financing for national HCV programs.

The current analysis further suggests that the current diagnostic and monitoring package could be substantially simplified as a result of the improved side-effect

profile and efficacy of DAA combinations observed in clinical trials. Monitoring with a full blood count plus clinical chemistry test (pretreatment and during treatment) could be sufficient to monitor for side effects and could cost in the region of US$22 per person. If treatment is not pangenotypic, HCV genotyping could be added to pretreatment monitoring.[10] Although qualitative viral load monitoring is desirable and informative, current approaches are expensive and technically complex; this limitation, together with the high SVR rates in current DAA trials, brings into question the necessity of repeated viral load monitoring during treatment. Given that the majority of HCV infections are associated with very high viral loads, including in patients relapsing after treatment, a qualitative HCV antigen test could be sufficient to confirm viral replication or suppression both pre- and post-treatment.[8,33,44] The HCV antigen assay is less expensive and requires less technical expertise than PCR assays; further evaluations regarding the LLOD are required.[40] New studies need to assess how often the RNA levels are above the LLOD of 2,000 IU/mL before treatment or at relapse/reinfection and to confirm that the HCV-RNA and HCV antigen tests provide comparable results.

This analysis has several limitations. The results of clinical trials on the new DAAs are not representative of all patient subpopulations in need of treatment. Relatively few patients with genotypes 4-6 have been included in clinical studies, despite these genotypes predominating in certain regions of the world.[8] The high SVR rates for these new DAAs still need to be confirmed in real-world situations outside clinical trials.[3] Most of these DAAs are only at phase III of development or have only recently been approved. Clinical trial populations are selective, and safety in program settings may be different. All regimen cost estimates in this analysis are based on a 12-week treatment course. Shorter treatment durations would further reduce estimated costs if efficacy is shown. Conversely, for some of the currently approved DAA regimens, some genotypes require 24 weeks of treatment. In the future, when clinical trial results are available, the costs of sequences of treatment will be required, including new or existing DAA treatments for patients who relapse on their initial combinations—these costings will need to be included in subsequent analyses. Finally, the estimated costs do not include the importation, transport, and distribution of the drugs.

The HCV pipeline includes several other promising candidates that may emerge as future treatment options.[8] For example the new drug, GS-5816, is clinically active against all genotypes. At a daily dose of 25-100 mg, a 12-week treatment course would only require between 2 and 8 g of API.

In summary, minimum costs of treatment and diagnostics to cure HCV were estimated at US$174-354 per person without genotyping and US$264-444 per person with genotyping. These costs assume that large-scale treatment programs can be established for HCV, similar to those implemented for HIV/acquired immune deficiency syndrome. Treatments with proven pangenotypic activity will be required to avoid expensive pretreatment genotyping, and further reductions in price could be achieved through shorter durations of treatment, if efficacy is proven.

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