

Minimum target prices for production of treatment and associated diagnostics for Hepatitis C in developing countries

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Introduction

Several combinations of direct-acting antivirals (DAAs) are being developed and licensed that can cure hepatitis C virus (HCV) in the majority of treatment naïve patients, in a range of genotypes.

Given that the burden of HCV falls mainly on low and middle income countries, treatment could be out of reach for most of those in need at the current prices.

In order to replicate the successes of providing antiretroviral therapy for treatment of HIV for over 10 million people in developing countries, the costs of HCV treatment and monitoring need to be very low.

This analysis aimed to estimate the minimum costs of DAA treatment and associated diagnostic monitoring.

Methods

Clinical trials of HCV DAAs were reviewed to identify combinations with consistently high rates of Sustained Virological Response (SVR) and pan-genotypic activity (Table 1).

For each DAA, molecular structures, doses, treatment duration, and components of retro-synthesis were used to estimate costs of mass production.

Manufacturing costs per gram of DAA were projected as formulated product cost, based upon treating at least 5 million patients/year (to arrive at volume demand) and a 40% margin for formulation.

Costs of diagnostic support were estimated based on published prices of tests from developing countries.

Table 1. Result from clinical trials – arms combined, treatment naïve, by genotype.

Combination	Trial	Genotype	Treatment arms	SVR rate
Daclatasvir + sofosbuvir	AI444-040	1	12wk (n=41)	95% (SVR-24)
	Combined 24wk arms	2&3	24wk (n=9)	97% (SVR-24)
		2&3	24wk (n=30)	93% (SVR-24)
Sofosbuvir + ribavirin	Combined QUANTUM & ELECTRON	1	12wk (n=69)	75% (SVR-12)
	Combined POSITRON, VALENCE, FISSION, & PHOTON-1	2	12wk (n=237)	94% (SVR-12)
	Combined POSITRON, FISSION, & PHOTON-1	3	12wk (n=323)	59% (SVR-12)
	Ruane et al.	4	12wk (n=14)	79% (SVR-12)
Sofosbuvir + ribavirin	Combined SPARE, QUANTUM, & PHOTON-1	1	24wk (n=168)	73% (SVR-12)
	VALENCE	3	24wk (n=105)	93% (SVR-12)
	Ruane et al.	4	24wk (n=14)	100% (SVR-12)
Sofosbuvir + ledipasvir	Combined LONESTAR & ION-3	1	8wk (n=235)	94% (SVR-12)
	Combined LONESTAR, ION-1, ION-3, SYNERGY, & ERADICATE	1	12wk (n=544)	95% (SVR-12)
	ION-1	1	24wk (n=217)	97% (SVR-12)
	ELECTRON-2 (Cohort 1)	3	12wk (n=25)	64% (SVR-12)
MK-8742 + MK-5172	C-WORTHY	1	12wk (n=103)	95% (SVR 4-24)
MK-5172	Combined 12wk arms			

Results

The drugs considered a high priority for the cost analysis were ledipasvir, MK-8742, and MK-5172. In addition, ribavirin, daclatasvir, and sofosbuvir have been previously evaluated to determine the lowest production costs [Ref 1].

The retro-synthesis and the active pharmaceutical ingredients (APIs) for these drugs are shown in Figure 1. These processes were analysed, and used to determine the lowest costs of producing each DAA.

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

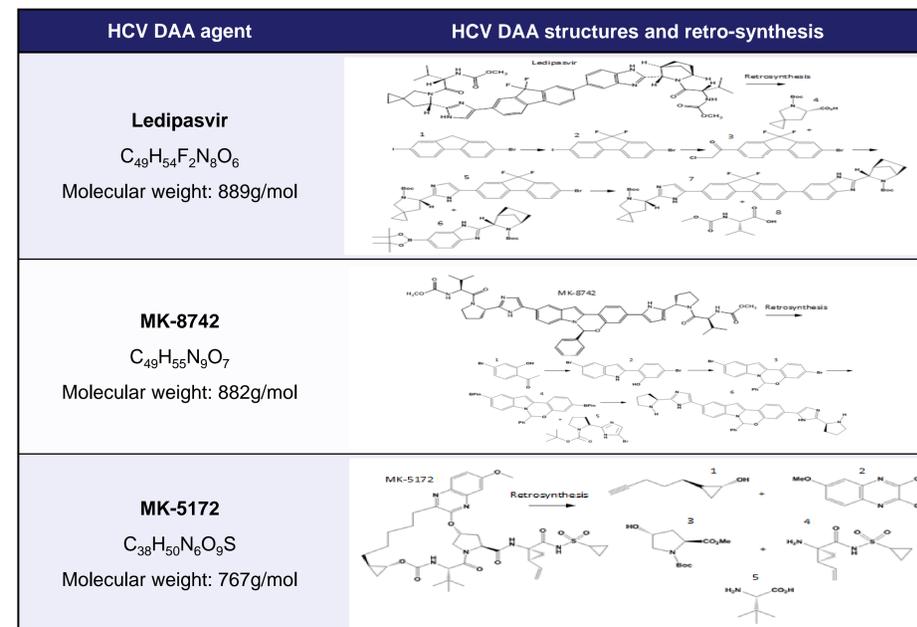


Table 2 shows the predicted minimum costs for a 12-week course of treatment with each DAA, along with the patent expiry dates. The predicted costs of treatment with key drug combinations are shown in Table 3.

Table 2. Predicted minimum costs of selected HCV DAAs for 12 weeks treatment.

*current mid-point cost of API from 3 Chinese suppliers – predicted cost is adjusted with a 40%

Agent	Patent expiry	Daily dose, mg	Overall dose per 12-wk, g	Estimated cost/g, US\$	Predicted cost, US\$
Ribavirin	Generic	1200	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

Table 3. Predicted costs of key drug combinations.

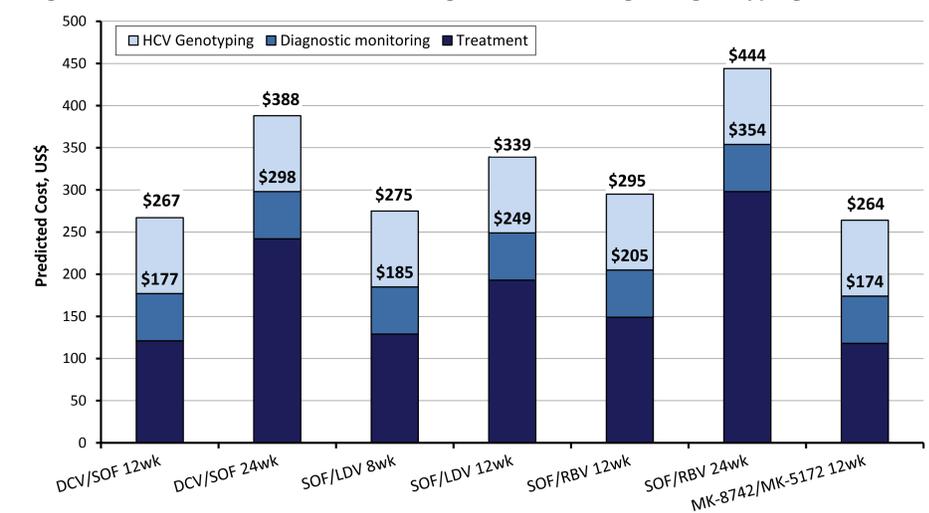
Combination treatment	Daily dose, mg	Duration, weeks	Predicted unit cost, US\$
MK-8742 + MK-5172	50+100	12	\$118
Daclatasvir + sofosbuvir	60+400	24	\$242
Sofosbuvir + ledipasvir	400+90	8	\$129
		12	\$193
Sofosbuvir + ribavirin	400+1200	12	\$149
		24	\$298

Results

The favorable safety profiles of these DAA combinations suggest that minimal laboratory monitoring will be necessary to assess safety during treatment. Diagnostics and monitoring could be limited to two HCV antigen tests to confirm infection and clearance after treatment (detection limit HCV RNA >2000 IU/mL; US\$34 for two tests), two full blood count and clinical chemistry tests (ALT and creatinine; US\$22), and genotyping if necessary (US\$90).

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

Figure 2. Minimum costs of treatment, diagnostic monitoring, and genotyping.



Limitations

More detailed analysis of the chemical synthesis and APIs and formulation is necessary to produce more accurate estimates of the commercial costs.

These cost estimates assume a large volume demand: over 1 million people treated per year. Support from donor agencies/governments is required to reach this demand.

The estimates assume that there is pressure in the market to lower costs of generic manufacture; while DAAs remain on patent, this generic competition may be limited.

The results of DAA clinical trials are not representative of all patient subpopulations and genotypes. Additionally, the high SVR rates need to be proven in real-world situations.

These estimates are based on a 12-week treatment course; 4- and 6-week courses are being evaluated in clinical trials. Furthermore, the HCV pipeline includes several other promising candidates that may be included in further analyses.

Conclusions

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 programmes can be established for Hepatitis C, similar to those implemented for HIV/AIDS.

Treatments with proven pan-genotypic activity will be required to avoid expensive pre-treatment genotyping, and further reductions in price could be achieved through shorter durations of treatment, if efficacy is proven.

This low cost treatment package could make universal access to HCV treatment in lower resource settings a realistic goal.

Literature cited

¹Hill A, Khoo S, Fortunak J, Simmons B, and Ford N. 2014. Minimum costs for producing hepatitis C direct-acting antivirals for use in large-scale treatment access programs in developing countries. Clin Infect Dis. 58(7):928-36.