Minimum costs to produce Hepatitis C Direct Acting Antivirals

Andrew Hill, Liverpool University, UK
Bryony Simmons, Imperial College, London, UK
Nikolien van de Van, Imperial College, London, UK
Nathan Ford, University of Cape Town, South Africa
Saye Khoo, Liverpool University, UK
Joe Fortunak, Howard University, Washington DC, USA

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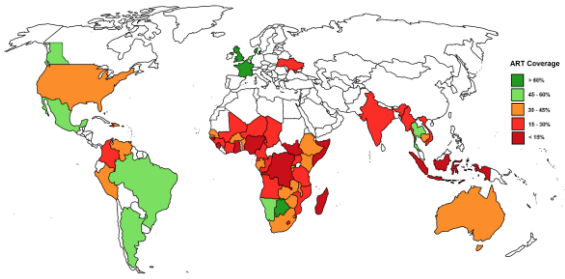
A key moment in the history of HIV

"My generics company can manufacture HIV antiretrovirals for a dollar per day"

Dr Yussef Hamied
Cipla,
G8 summit,
2000

The percentage of all HIV-infected people on antiretroviral treatment, by country (10 million treated)



Andrew Hill et al. World AIDS Conference 2014 [LBPE29]

Rationale

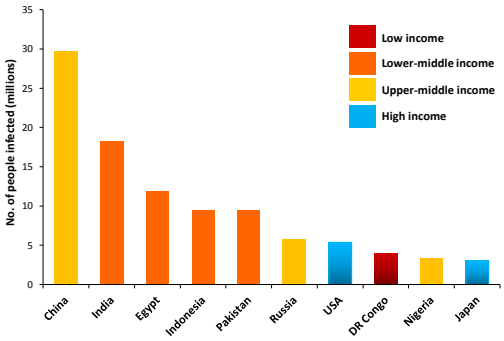
Generic antiretrovirals are currently manufactured at very low cost, for treatment of over ten million people with HIV in low and middle-income countries.

DAAs for HCV infection have similar mechanisms of action and chemical structures to antiretrovirals for HIV infection.

For widespread treatment of HCV in developing countries to be feasible, we need short-course of antiviral treatment available at very low cost.

Using the cost of HIV drugs as a framework, we can make estimates for the potential cost of HCV DAAs.

Hepatitis C global prevalence by country (2010)



Aims

The aim was to estimate the minimum cost of HCV treatment

Three assumptions:

1. The same methods of generic manufacturing used to supply antiretrovirals to people with HIV/AIDS in developing countries.

2. No patent restrictions on mass drug production

3. Procurement of large orders for drug manufacture by generic companies (over 5 million people treated).

METHODS – SELECTION OF DAAS FOR ANALYSIS

Clinical trials of HCV DAAs were reviewed to identify combinations with:

- Phase 2 or 3 trial results available
- Consistently high rates of Sustained Virological Response (SVR)
- Safety data available
- Future program of clinical trials in different genotypes

Patent expiry dates were found for all DAAs in this analysis

SVR RATES

SVR rates in naïve patients given DAA combinations, by genotype and duration of treatment.

Results combined across clinical trials

Combination	Trial	Genotype	Treatment arms	SVR rate
Daclatasvir + sofosbuvir	AI444-040	1	12wk (n=41)	95% (SVR-24)
	Combined 24wk arms		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 Combined 12wk arms	1	12wk (n=103)	95% (SVR 4-24)

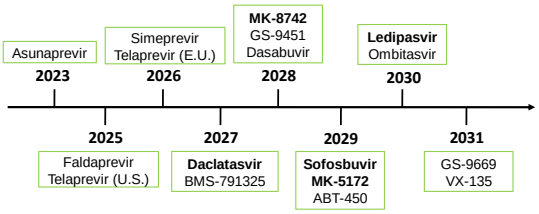
HCV DRUG DEVELOPMENT: DIRECT ACTING ANTIVIRALS

DAAs in Phase II and Phase III trials:

Nucleoside and nucleotide polymerase inhibitors	NS5a inhibitors	HCV protease inhibitors	Non-nucleoside polymerase inhibitors
Sofosbuvir	**Daclatasvir**	Asunaprevir	ABT-072
Mericitabine	ABT-267	Faldaprevir	ABT-333
	Ledipasvir (GS-5885)	Simeprevir	BI 207127
	GSK2336805	Vaniprevir	BMS-791325
	MK-8742	ABT-450/r	Setrobuvir
		Sovaprevir	Tegobuvir
		Danoprevir/r	VX-222
		GS-9256	
		GS-9451	
		MK-5172	

The drugs in **bold** have been highlighted as most promising for large-scale treatment programmes in low or middle-income countries.

Patent Expiry Dates of DAAs



Methods – calculation of treatment costs

For each selected DAA, costs of mass production were estimated from:

- molecular structures,
- doses,
- treatment duration,
- components of retro-synthesis, with costs of API (active product ingredient)
- 40% margin for formulation (including profit margin for generic supplier).

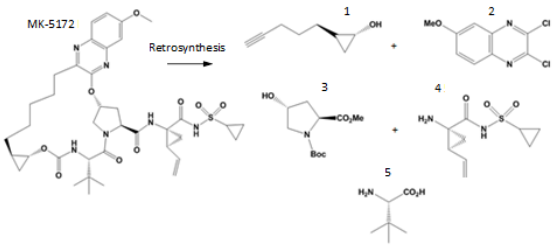
Manufacturing costs per gram of DAA were projected as formulated product cost, based upon treating at least 5 million patients/year (to arrive at volume demand)

Retro-synthesis of MK-5172

MK-5172

$C_{38}H_{50}N_6O_9S$

Molecular weight: 767g/mol

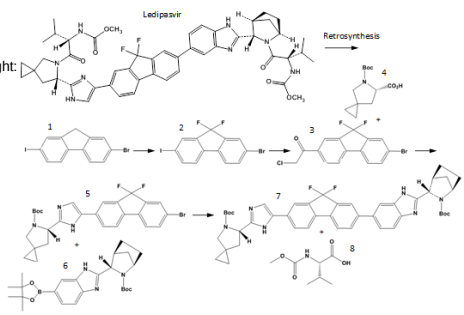


Retro-synthesis of ledipasvir

Ledipasvir

$C_{49}H_{54}F_2N_8O_6$

Molecular weight: 889g/mol



HIV Nucleos(t)ide inhibitors

Agent	Chemical formula	Molecular weight	Daily dose (mg)	Dose per year (g)	Cost per gram ($)	Cost per year ($)
ABC	$C_{14}H_{18}N_6O$	286	600	219	**$0.77**	$169
FTC	$C_8H_{10}FN_3O_3S$	247	200	73	**$0.79**	$58
d4T	$C_{10}H_{12}N_2O_4$	224	60	22	**$0.86**	$19
ZDV	$C_{10}H_{13}N_5O_4$	267	600	219	**$0.34**	$75
3TC	$C_8H_{11}N_3O_3S$	229	300	110	**$0.19**	$21
TDF	$C_{23}H_{34}N_5O_{14}P$	636	300	110	**$0.52**	$57

*Converted in to dose per year (g) by (daily dose(mg)/1000)x365
Source: Médecins Sans Frontières. Untangling the web of antiretroviral price reductions. 15th Edition – July 2012. http://utw.msfaccess.org/

HIV Protease inhibitors – production costs

Agent	Chemical formula	Molecular weight	Daily dose (mg)	Dose per year (g)	Cost per gram ($)	Cost per year ($)
Atazanavir	$C_{38}H_{52}N_6O_7$	705	300	110	**$2.11**	$231
Lopinavir/r	$C_{37}H_{48}N_4O_5$	629	800/200 = 1000	365	**$1.01**	$368
Darunavir	$C_{27}H_{37}N_3O_7S$	548	1200	438	**$1.83**	$803
Indinavir	$C_{36}H_{47}N_5O_4$	614	1600	584	**$0.67**	$394
Saquinavir	$C_{38}H_{50}N_6O_5$	671	2000	730	**$1.87**	$1366

*Converted in to dose per year (g) by (daily dose(mg)/1000)x365
Source: Médecins Sans Frontières. Untangling the web of antiretroviral price reductions. 15th Edition – July 2012. http://utw.msfaccess.org/

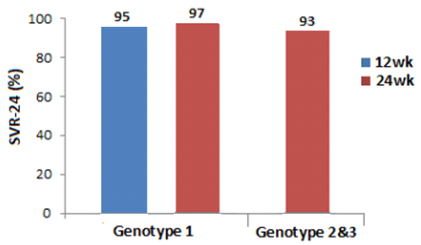
COSTS PER PERSON, FOR 12 WEEK COURSE OF HCV DAA

Agent	Daily Dose (mg)	Overall dose for 12wks (g)	Production cost estimate ($/g)	Predicted cost ($)
Ribavirin	1200	101	**$0.34***	$48
Daclatasvir	60	5	**$4.0**	$20
Sofosbuvir	400	34	**$3.0**	$101
MK-8742	50	4	**$11.0**	$44
MK-5172	100	8	**$8.9**	$74
Ledipasvir	90	8	**$11.6**	$93

* current mid-point cost of API from 3 Chinese suppliers
**shows cost for 1200mg daily dose; $41 for 1000mg daily dose of ribavirin

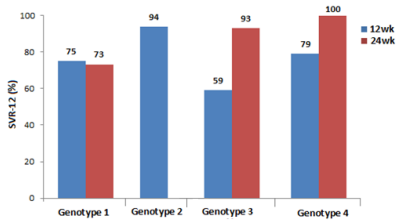
DACLATASVIR + SOFOSBUVIR COMBINATION TREATMENT

Regimen	Duration (weeks)	Predicted unit cost of combination HCV treatment (US$)	Predicted cost for 5 million people (US$ millions)
Daclatasvir + Sofosbuvir	12	**$122**	610



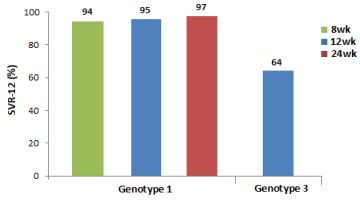
SOFOSBUVIR + RIBAVIRIN COMBINATION TREATMENT

Regimen	Duration (weeks)	Predicted unit cost of combination HCV treatment ($)	Predicted cost for 5 million people (US$ millions)
Sofosbuvir + Ribavirin	12	**$152**	760
Sofosbuvir + Ribavirin	24	**$304**	1,520



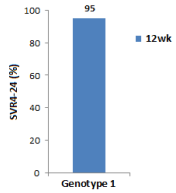
SOFOSBUVIR + LEDIPASVIR COMBINATION TREATMENT

Regimen	Duration (weeks)	Predicted unit cost of combination HCV treatment ($)	Predicted cost for 5 million people (US$ millions)
Sofosbuvir + Ledipasvir	8	**$130**	650
Sofosbuvir + Ledipasvir	12	**$195**	975



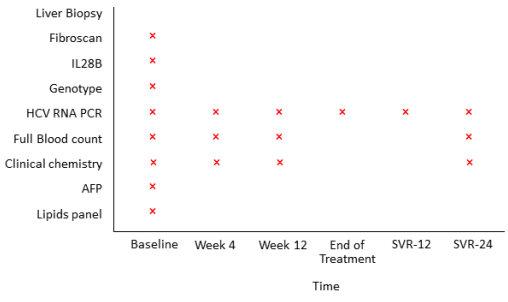
MK-8742 + MK-5172 COMBINATION TREATMENT

Regimen	Duration (weeks)	Predicted unit cost of combination HCV treatment (US$)	Predicted cost for 5 million people (US$ millions)
MK-8742 + MK-5172	12	**$115**	575



DIAGNOSTIC TESTING IN HCV

At present, HCV diagnosis and monitoring is complex, requiring a number of different tests.



Adapted from the European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatitis c virus infection.

HCV DIAGNOSTIC TESTING – THE FUTURE?

If treatments are pan-gentotypic, do we still need genotyping pre-treatment?

If treatments work in >90% of people, do we still need to evaluate predictors of response (IL-28B, AFP, baseline HCV RNA)?

If DAA combinations work in >90% of people, do we still need on-treatment monitoring of HCV RNA by PCR?

Genotyping and HCV RNA PCR are expensive and complex to include in mass treatment programmes.

HCV antigen assays have lower detection limits of 2000 IU/mL – is this low enough to detect either chronic infection (before treatment) and lack of relapse or re-infection (6-12 months post treatment)?

HCV genotypes 1-6 worldwide

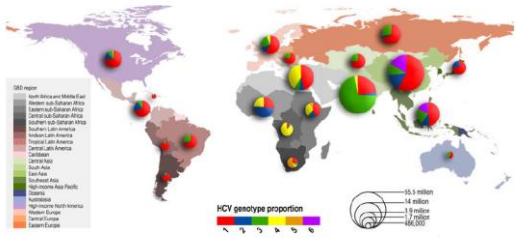
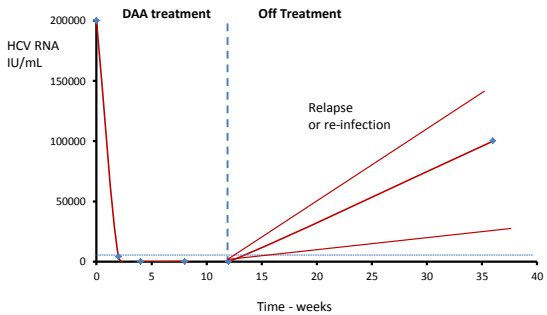


Fig. 1. Relative prevalence of each HCV genotype by GBD region. Size of pie charts is proportional to the number of seroprevalent cas

HCV RNA profiles during treatment



HCV DIAGNOSTIC TESTING – THE FUTURE?

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 counts + clinical chemistry tests (AST / platelets): US$22

- genotyping if necessary: US$90 (not needed if treatment is pan-genotypic)

COMBINED COSTS – SOFOSBUVIR + DACLATASVIR

Cost of sofosbuvir: $101 (12 weeks)

Cost of daclatasvir: $20 (12 weeks)

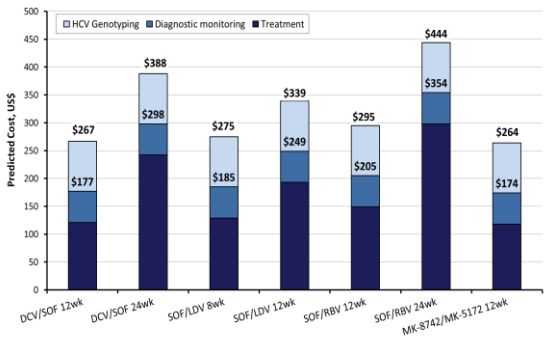
- two HCV antigen tests: US$34 (max)

- Lab safety: US$22 (two FBC / Clin Chem)

Total cost of treatment and care: US $177

- Additional genotyping if necessary: US$90 (not needed if treatment is pan-genotypic)

PROJECTED MINIMUM COSTS FOR TREATMENT AND DIAGNOSTICS



Limitations of the analysis

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 5 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.