Minimum costs to produce Hepatitis C Direct Acting Antivirals

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TREATMENT COVERAGE IS LOW EVEN IN DEVELOPED COUNTRIES

Despite the long-term morbidity & mortality associated with untreated hepatitis C, data suggests that relatively few patient are being treated.

In Europe only **3.5% of infected individuals** received antiviral treatment by the end of 2010

(ranging from 16% in France to <1% in Poland)

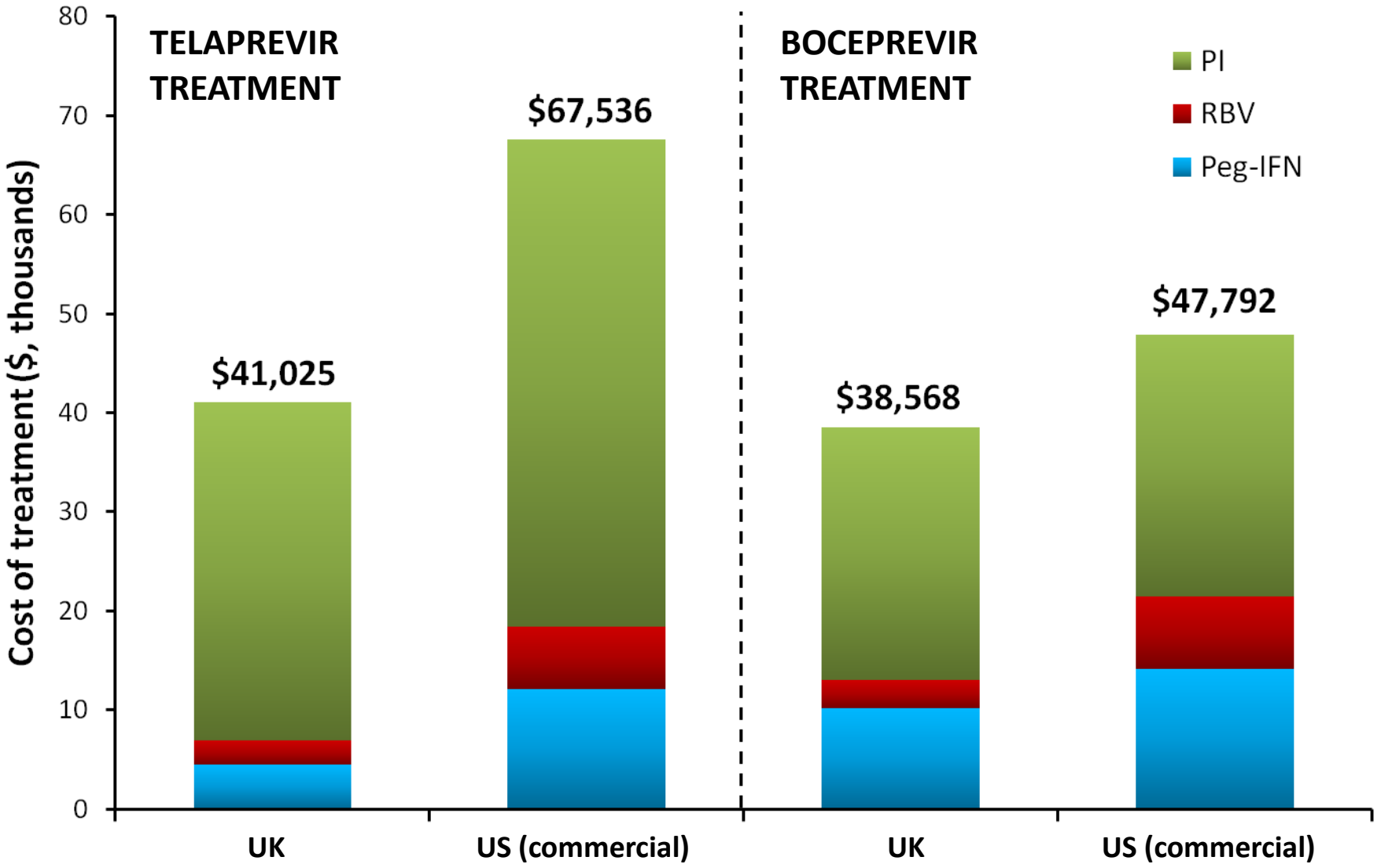
In the USA only **21% of infected individuals** had received treatment by the end of 2007

Reasons for under-treatment:

- Under-diagnosis (80% of HCV cases are asymptomatic)
- Limitations of currently available medication
- The very high prices of drug treatment

Data taken from: Antiviral therapy for hepatitis C: why are so few patients being treated? (J Antimicrob Chemother. 2010;65:1327-1329)
HCV treatment rate in select European countries in 2004-2010. (J Hepatol. 2013;58(suppl 1):S22-23)

ESTIMATED COST OF CURRENT TREATMENT (UK & US ESTIMATES)



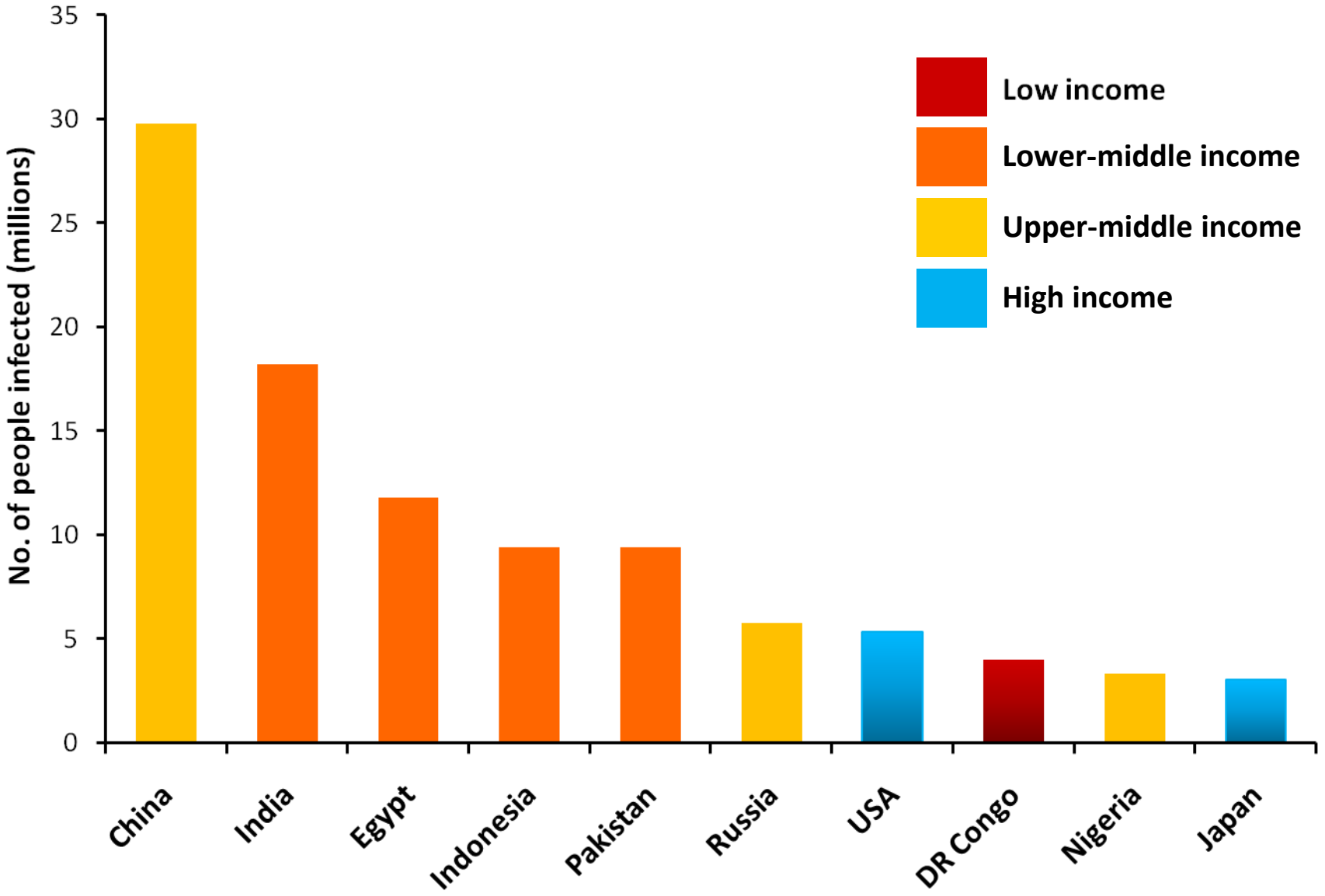
Source: Ziad F, et al. 62nd AASLD; San Francisco, CA; Novermber 04-08, 2011. Abst. 118.

Hepatitis C global prevalence by country (2010)

Country	Income classification	Most prevalent genotypes	Anti-HCV (%)	No. infected
China	Upper-middle	1,2,6	2.2	29,791,212
India	Lower-middle	1,3	1.5	18,216,960
Egypt	Lower-middle	4	14	11,826,360
Indonesia	Lower-middle	1,2	3.9	9,436,986
Pakistan	Lower-middle	3	5.9	9,422,403
Russia	Upper-middle	1,3	4.1	5,796,498
USA	High	1,2,3	1.8	5,367,834
Democratic Republic of Congo	Low	4	6.4	4,010,240
Nigeria	Lower-middle	1,2	2.1	3,323,439
Japan	High	1,2	2.4	3,058,008
Cameroon	Lower-middle	1,2,4	13.8	2,754,204
Brazil	Upper-middle	1,3	1.4	2,609,670
Uganda	Low	1,4	6.6	2,230,536
Philippines	Lower-middle	1	2.2	1,932,854
Italy	High	1,2	3.2	1,923,136
Ukraine	Lower-middle	1	4	1,864,840
Uzbekistan	Lower-middle	1,3	6.5	1,774,955
Turkey	Upper-middle	1	2.2	1,549,108
Ethiopia	Low	1,2,4	1.9	1,500,734
Thailand	Upper-middle	1,3,6	2.2	1,499,058
World's Population			**2-3%**	**130-170 million**

Source: Evolving epidemiology of hepatitis C virus (Clin Microbiol Infect. 2011; 17(2): 107-115). Income classification from The World Bank, 2013.

Hepatitis C global prevalence by country (2010)



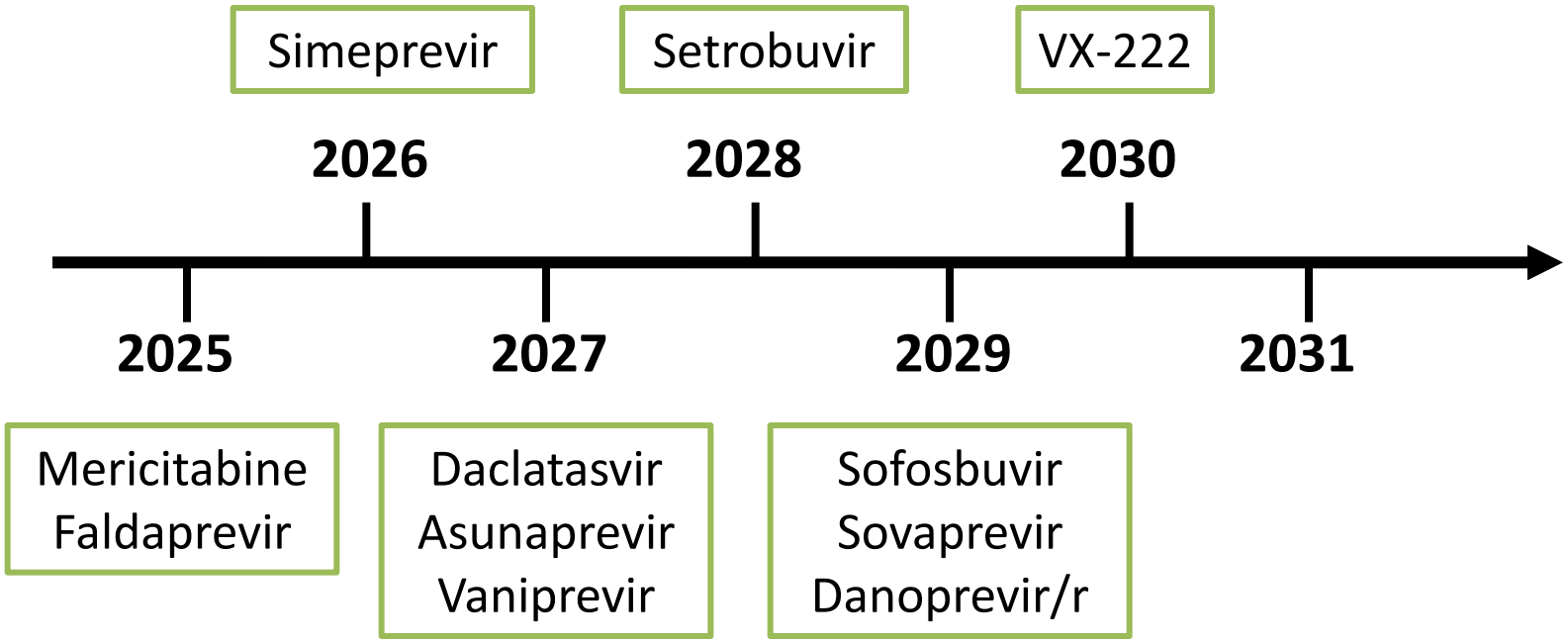
HCV DRUG DEVELOPMENT: INTERFERON-FREE REGIMENS

A number of promising DAAs are undergoing 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
	IDX-719	ABT-450/r	Setrobuvir
		Sovaprevir	Tegobuvir
		Danoprevir/r	VX-222
		GS-9256	
		GS-9451	
		MK-5172	

The drugs in **bold** have been highlighted as those next likely to be approved for treatment of hepatitis C.
These drugs are not only being developed with Peg-IFN/RBV, but also with other DAAs in interferon-free trials.

Patent expiry dates



Whilst the patent on RBV has already expired, the US patents covering Peg-IFN are due to expire in ***Jan 2015 (PEGINTRON)*** & ***2018 (Pegasys)***

DAA combinations: Interferon-free regimens

Several combinations of two DAAs (with or without RBV) can cure HCV (SVR) in the majority of treatment-naïve, genotype 1 patients, without the use of interferon:

Combination	Study population	Previous response	Geno-type	Treatment arms	SVR rate
Daclatasvir + sofosbuvir +/- RBV	AI444-040 Non-cirrhotic (n=170)	Naïve	1	12wk (n=82)	**95-98%** (SVR-4)
				24wk (n=44)	**93-100%** (SVR-24)
			2&3	24wk (n=44)	**88-100%** (SVR-24)
Daclatasvir + asunaprevir + BMS-791325	AI443-014 Non-cirrhotic (n=32)	Naïve	1	24wk (n=16)	**94%** (SVR-4)
				12wk (n=16)	**94%** (SVR-12)
Daclatasvir + asunaprevir	AI447-011 (n=38)	Null	1b	Once-daily (n=20)	**65%** (SVR-12)
				Twice-daily (n=18)	**78%** (SVR-12)
Sofosbuvir + RBV +/- GS-5885	ELECTRON Non-cirrhotic (n=119)	Naïve	1	12wk, 3-drug (n=25)	**100%** (SVR-4)
				12wk, 2-drug (n=25)	**84%** (SVR-12)
		Null		12wk, 3-drug (n=9)	**100%** (SVR-4)
		Naïve	2&3	12wk, 2-drug (n=10)	**100%** (SVR-24)
				8wk, 2-drug (n=25)	**64%** (SVR-12)
		Experienced		12wk, 2-drug (n=25)	**68%** (SVR-12)

DAA COMBINATIONS: INTERFERON-FREE REGIMENS (CONT.)

Combination	Study population	Previous response	Geno-type	Treatment arms	SVR rate
Sofosbuvir + weight-based RBV or low-dose RBV	SPARE Non-cirrhotic (n=10) All stages fibrosis (n=50)	Naïve	1	24wk, non-cirrhotic, WB (n=10)	**90%** (SVR-12)
				24wk, WB (n=25)	**72%** (SVR-4)
				24wk, LD (n=25)	**56%** (SVR-4)
Sofosbuvir + RBV	POSITRON (n=402 +71 placebo)	Naïve	2	12wk (n=120)	**93%** (SVR-12)
			3	12wk (n=87)	**61%** (SVR-12)
		Experienced	2/3	12wk (n=100)	**50%** (SVR-12)
				16wk (n=95)	**73%** (SVR-12)
Sofosbuvir + simeprevir +/- RBV	COSMOS Non-cirrhotic (n=80)	Null response	1	24wk, 3-drug (n=24)	**67%** (SVR-8)
				24wk, 2-drug (n=15)	**100%** (SVR-8)
				12wk, 3-drug (n=27)	**96%** (SVR-8)
				12wk, 2-drug (n=14)	**93%** (SVR-8)
Faldaprevir + BI207127 +/- RBV	SOUND-C2 (n=329 [33=F4])	Naïve	1	28wk, 3-drug (n=316)	**up to 69%** (SVR-12)
				28wk, 2-drug (n=46)	**39%** (SVR-12)

Source: i-Base/Treatment Action Group. 2012 Pipeline Report: HIV, HCV, and TB drugs, diagnostics, vaccines, and preventative technologies in development. July 2012. http://www.pipelinereport.org/toc - for individual sources see references.

RATIONALE

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

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

Minimum costs of HIV antiretrovirals are $0.2-0.9/g of drug for nucleoside analogues, $0.5/g for nucleotide analogues, and $0.7-2.1/g for protease inhibitors.

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.

HIV Nucleos(t)ide inhibitors

Agent	Chemical formula	Molecular weight	Daily dose (mg)	Dose per year (g)	Cost per gram ($)	Cost per year ($)
Abacavir	$C_{14}H_{18}N_6O$	286	600	219	$0.77	$169
Emtricitabine	$C_8H_{10}FN_3O_3S$	247	200	73	$0.79	$58
Stavudine	$C_{10}H_{12}N_2O_4$	224	60	22	$0.86	$19
Zidovudine	$C_{10}H_{13}N_50_4$	267	600	219	$0.34	$75
Lamivudine	$C_8H_{11}N_3O_3S$	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

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/ritonavir	$C_{37}H_{48}N_4O_5$	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/

METHODS

The aim was to estimate the minimum cost of HCV treatment, assuming the same methods of manufacturing as used to supply antiretrovirals to people with HIV/AIDS in developing countries. This assumes no patent restrictions on production, and procurement of large orders for drug manufacture by generic companies.

HCV DAAs currently in Phase 2 or 3 development were matched by molecular weight, chemical structure, and dose to the closest equivalent antiretroviral.

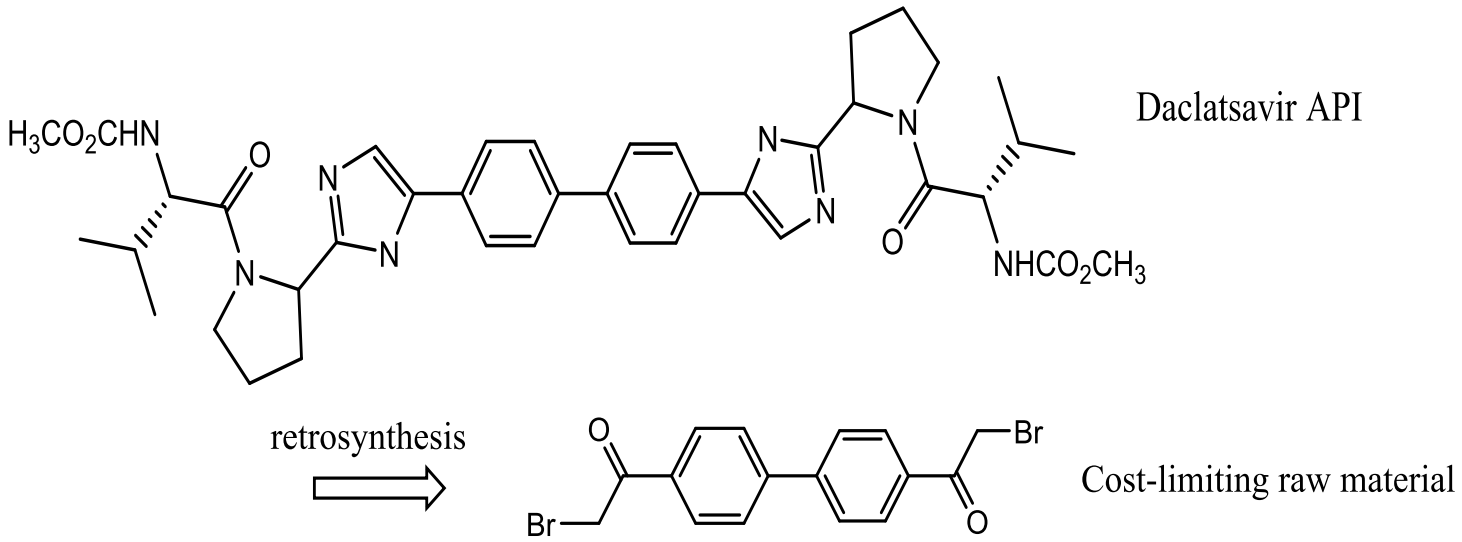
The total drug requirement for a 12 week (84 day) course of each HCV DAA (in grams) was calculated & using this, the minimum cost of treatment with each HCV DAA was calculated (for 12 weeks treatment).

The production cost per gram of drug was assumed to be between 1-10 times higher than the equivalent HIV antiretroviral, depending on the complexity of chemical synthesis.

HCV DAAs SUMMARY

Agent	Molecular Weight (g/mol)	Daily Dose (mg)	Overall dose for 12wks (g)	Class of treatment	Patent expiry
Ribavirin	244	1000-1200mg	84-101g	Nucleoside analogue	Generic
Daclatasvir	739	60mg	5g	NS5A inhibitor	2027
Sofosbuvir	529	400mg	34g	Nucleotide	2029
Faldaprevir	870	120mg	10g	Protease inhibitor	2025
Simeprevir	750	150mg	13g	Protease inhibitor	2026

DACLATASVIR



HCV: Daclatasvir

$C_{40}H_{50}N_8O_6$

Molecular weight: 739 g/mol

Class: NS5A inhibitor

5g per treatment course

HIV: Atazanavir

$C_{38}H_{52}N_6O_7$

Molecular weight: 705 g/mol

Class: protease inhibitor

$2.11 per gram

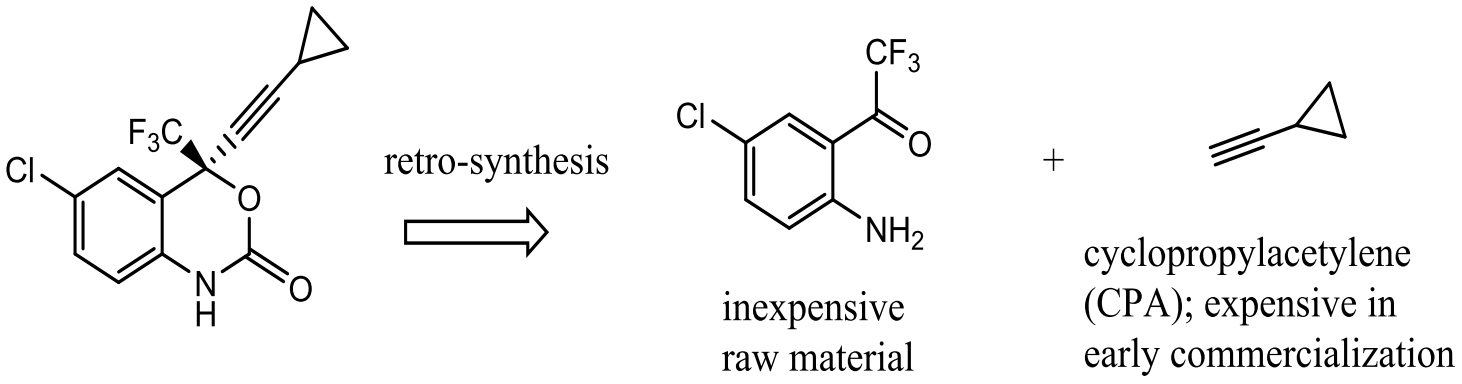
DACLATASVIR

Daclatasvir is an NS5A inhibitor, and appears to have a straightforward synthesis, given its symmetry and the availability of cheap starting materials to synthesise the side-chains.

HIV drug	HIV cost per gram ($)	Complexity of HCV synthesis	HCV production cost estimate (per g)	HCV dose per treatment (g)	Potential cost of HCV drug for 12wk course ($)
ATV	$2.11	x3	$6 per g	5g	$30
IDV	$0.67	x3	$2 per g	5g	$10
SQV	$1.87	x3	$6 per g	5g	$30

Complexity of chemical synthesis is approximately 3 times the HIV cost per gram; estimates for daclatasvir are conservative

SOFOSBUVIR



HCV: Sofosbuvir

$C_{22}H_{29}FN_3O_9P$

Molecular weight: 529 g/mol

Class: nucleotide

34g per treatment course

HIV: Tenofovir disoproxil fumarate (TDF)

$C_{23}H_{34}N_5O_{14}P$

Molecular weight: 636 g/mol

Class: NtRTI

$0.52 per gram

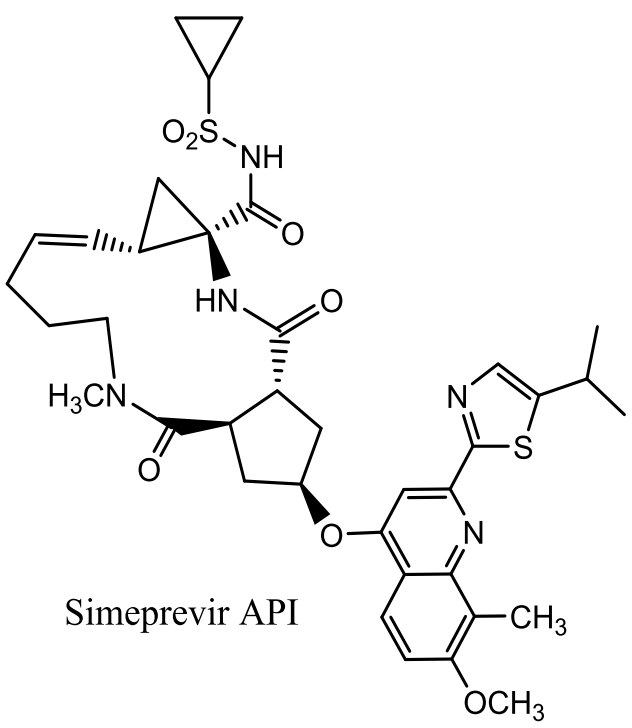
SOFOSBUVIR

Sofosbuvir is a nucleotide with requires a chiral 2'-fluro-2'-methylfuranose intermediate complicating synthesis.

HIV drug	HIV cost per gram ($)	Complexity of HCV synthesis	HCV production cost estimate (per g)	HCV dose per treatment (g)	Potential cost of HCV drug for 12wk course ($)
d4T	$0.96	x4	$4 per g	34g	$136
TDF	$0.52	x4	$2 per g	34g	$68

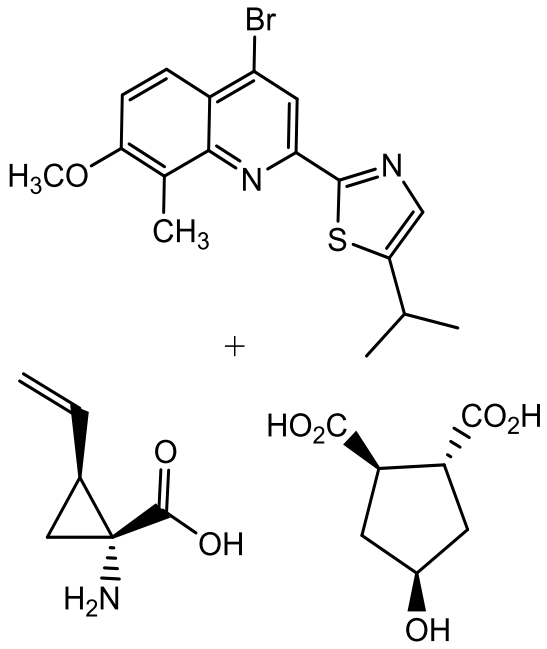
Complexity of chemical synthesis is approximately 4 times the HIV cost per gram

SIMEPREVIR



Simeprevir API

retrosynthesis



Critical Raw Materials

HCV: Simeprevir

$C_{38}H_{47}N_5O_7S_2$

Molecular weight: 750 g/mol

Class: protease inhibitor

13g per treatment course

HIV: Lopinavir/r

$C_{37}H_{48}N_4O_5$

Molecular weight: 629 g/mol

Class: protease inhibitor

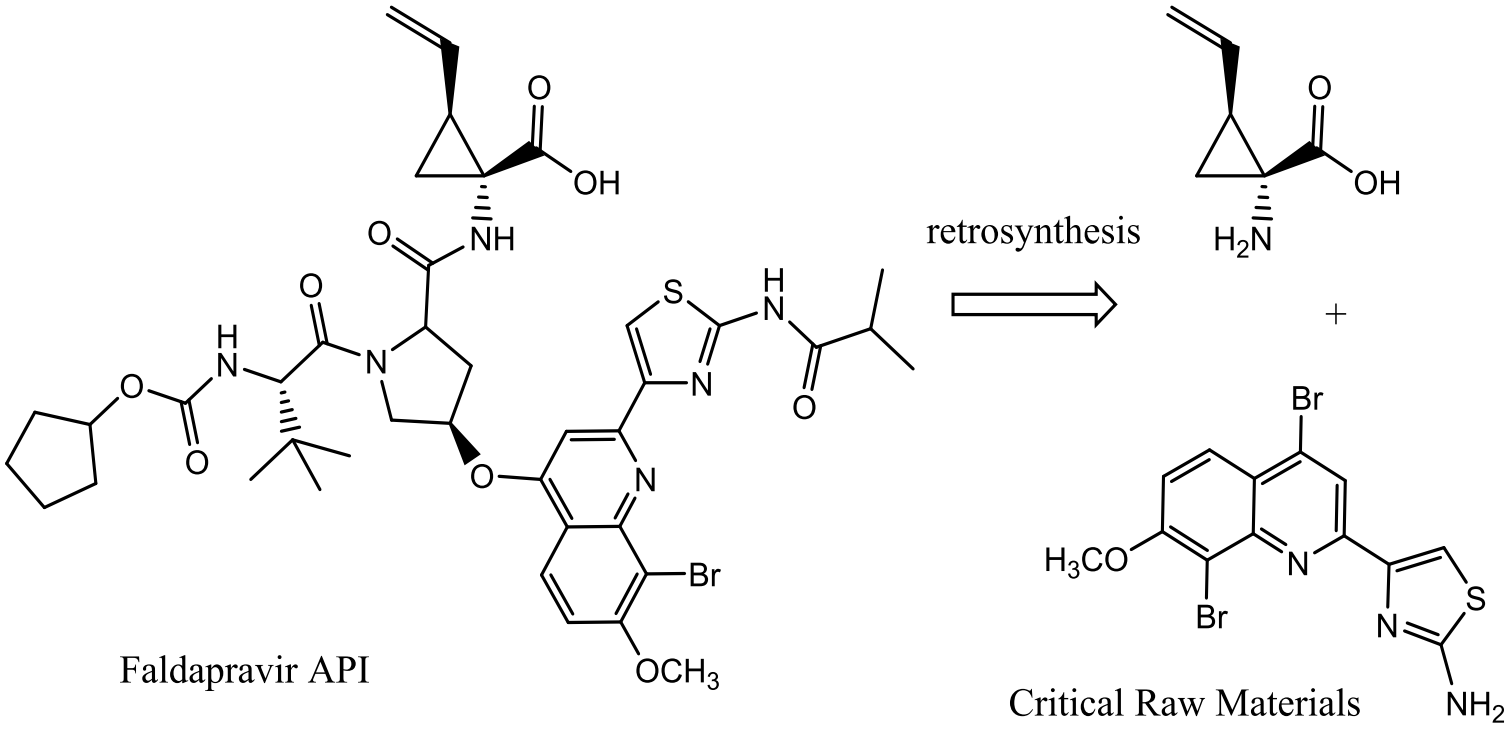
$1.01 per gram

SIMEPREVIR

Simeprevir is a protease inhibitor, which includes a macrocycle with chirality and an embedded chiral cyclopropane: this significantly complicates synthesis.

HIV drug	HIV cost per gram ($)	Complexity of HCV synthesis	HCV production cost estimate (per g)	HCV dose per treatment (g)	Potential cost of HCV drug for 12wk course ($)
ATV	$2.11	x10	$21 per g	13g	$270
LPV/r	$1.01	x10	$10 per g	13g	$130

FALDAPREVIR



HCV: Faldaprevir

$C_{40}H_{49}BrN_6O_9S$

Molecular weight: 870 g/mol

Class: protease inhibitor

10-20g per treatment course

HIV: Darunavir

$C_{27}H_{37}N_3O_7S$

Molecular weight: 548 g/mol

Class: protease inhibitor

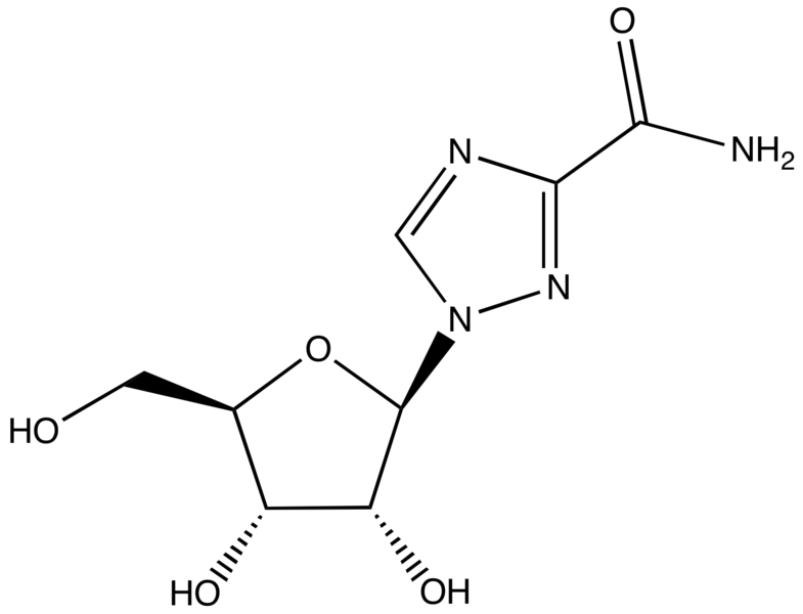
$1.83 per gram

Faldaprevir

Faldaprevir is a protease inhibitor, which has a chiral cyclopropane, hydroxy propinyl unit: this complicates the chemical synthesis.

HIV drug	HIV cost per gram ($)	Complexity of HCV synthesis	HCV production cost estimate (per g)	HCV dose per treatment (g)	Potential cost of HCV drug for 12wk course ($)
ATV	$2.11	x10	$21 per g	10g	$210
DRV	$1.83	x10	$18 per g	10g	$180
LPV/r	$1.01	x10	$10 per g	10g	$100

Ribavirin



HCV: Ribavirin

$C_8H_{12}N_4O_5$

Molecular weight: 244 g/mol

Class: nucleoside analogue

84g per treatment course

HIV: Zidovudine

$C_{10}H_{13}N_5O_4$

Molecular weight: 267 g/mol

Class: NRTI

$0.34 per gram

Ribavirin

Ribavirin is a nucleoside analogue, with a relatively simple chemical structure.

HIV drug	HIV cost per gram ($)	Complexity of HCV synthesis	HCV production cost estimate (per g)	HCV dose per treatment (g)	Potential cost of HCV drug for 12wk course ($)
d4T	$0.96	x1	$0.96 per g	84g	$81
ZDV	$0.34	x1	$0.34 per g	84g	$29
ABC	$0.77	x1	$0.77 per g	84g	$65

An analysis of the chemical synthesis of ribavirin showed a more accurate estimation of production cost per gram to be between $0.25 and $0.75, giving potential costs of $21-$63 for 1000mg per day, and $25-$76 for 1200mg per day.

Minimum Costs per person, for 12 week course of HCV DAAs

Agent	Daily Dose (mg)	Overall dose for 12wks (g)	Production cost estimate ($/g)	Predicted cost ($)
Ribavirin	1000-1200 mg	84-100g	$0.25-0.75 per g	$21-63*
Daclatasvir	60 mg	5g	$2-6 per g	$10-30
Sofosbuvir	400 mg	34g	$2-4 per g	$68-136
Faldaprevir	120 mg	10g	$10-21 per g	$100-210
Simeprevir	150 mg	13g	$10-21 per g	$130-270

*shows cost for 1000mg daily dose; $25-76 for 1200mg daily dose of ribavirin

POTENTIAL COSTS OF HCV COMBINATION TREATMENT

Study/drug	Length of treatment	Potential cost of HCV treatment ($)	Total cost of HCV treatment ($)
A1444-040 Daclatasvir + sofosbuvir (+/- RBV)	12-week	Daclatasvir = $10-30 Sofosbuvir = $68-136	$78-166
	24-week	Daclatasvir = $20-60 Sofosbuvir = $136-272	$156-332
POSITRON Sofosbuvir + RBV	12-week	Sofosbuvir = $68-136 RBV = $21-63	$89-199
	16-week	Sofosbuvir = $91-181 RBV = $28-84	$119-265
COSMOS Sofosbuvir + simeprevir +/- RBV	12-week (3-drug)	Sofosbuvir = $68-136 Simeprevir = $130-270 RBV = $21-63	$219-469
	12-week (2-drug)	Sofosbuvir = $68-136 Simeprevir = $130-270	$198-406

Potential costs of HCV combination treatment

Regimen	Duration (weeks)	Predicted cost of combination HCV treatment ($)
Daclatasvir + Sofosbuvir	12	$78-166
Daclatasvir + Sofosbuvir	24	$156-332
Daclatasvir + Sofosbuvir + Ribavirin	12	$99-229
Daclatasvir + Sofosbuvir + Ribavirin	24	$198-458
Sofosbuvir + Ribavirin	12	$89-199
Sofosbuvir + Ribavirin	16	$119-265
Sofosbuvir + Ribavirin	24	$178-398
Sofosbuvir + Simeprevir	12	$198-406
Sofosbuvir + Simeprevir	24	$396-812
Sofosbuvir + Simeprevir + Ribavirin	12	$219-469
Sofosbuvir + Simeprevir + Ribavirin	24	$438-938

Limitations of the analysis

More precise estimates of production costs require pilot production batches and more detailed analysis of process chemistry.

Access to HCV DAAs at minimum prices in developing countries will depend on the level of enforcement of patent restrictions.

Costs of production of HIV antiretrovirals have fallen progressively in the past 5 years. Costs of production of HCV DAAs may also decrease over time. The predicted costs for DAAs in this analysis are far higher than for HIV antiretrovirals.

The DAAs discussed in this analysis have mainly been evaluated in genotype 1 HCV, with limited clinical experience in genotypes 2 and 3.

There are other DAAs in earlier stages of development, which could be included in future analyses of minimum drug prices.

Conclusions

Within the next 15 years, large-scale manufacture of ribavirin plus two generic HCV DAAs is feasible, with target prices of $100-$250 per 12 week treatment course (for genotype 1 HCV infection).

Further progressive reductions in these costs may be possible through optimisation of chemical synthesis and cheaper sourcing of raw materials.

These low prices could make widespread access to HCV treatment in low and middle income countries, and potentially even HCV eradication, a realistic goal.

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