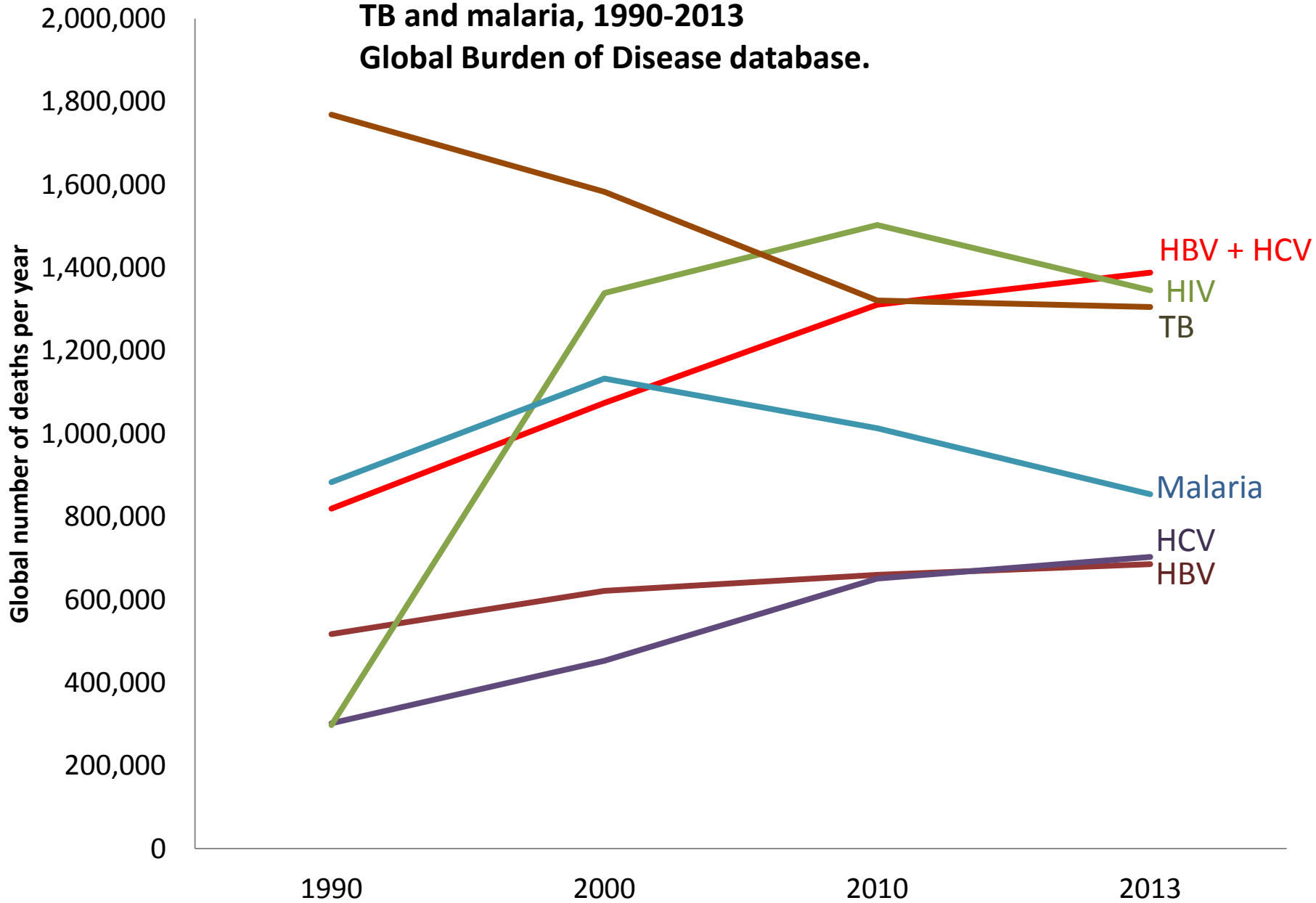


# **Minimum costs to treat viral hepatitis**

Andrew Hill  
Liverpool University, UK

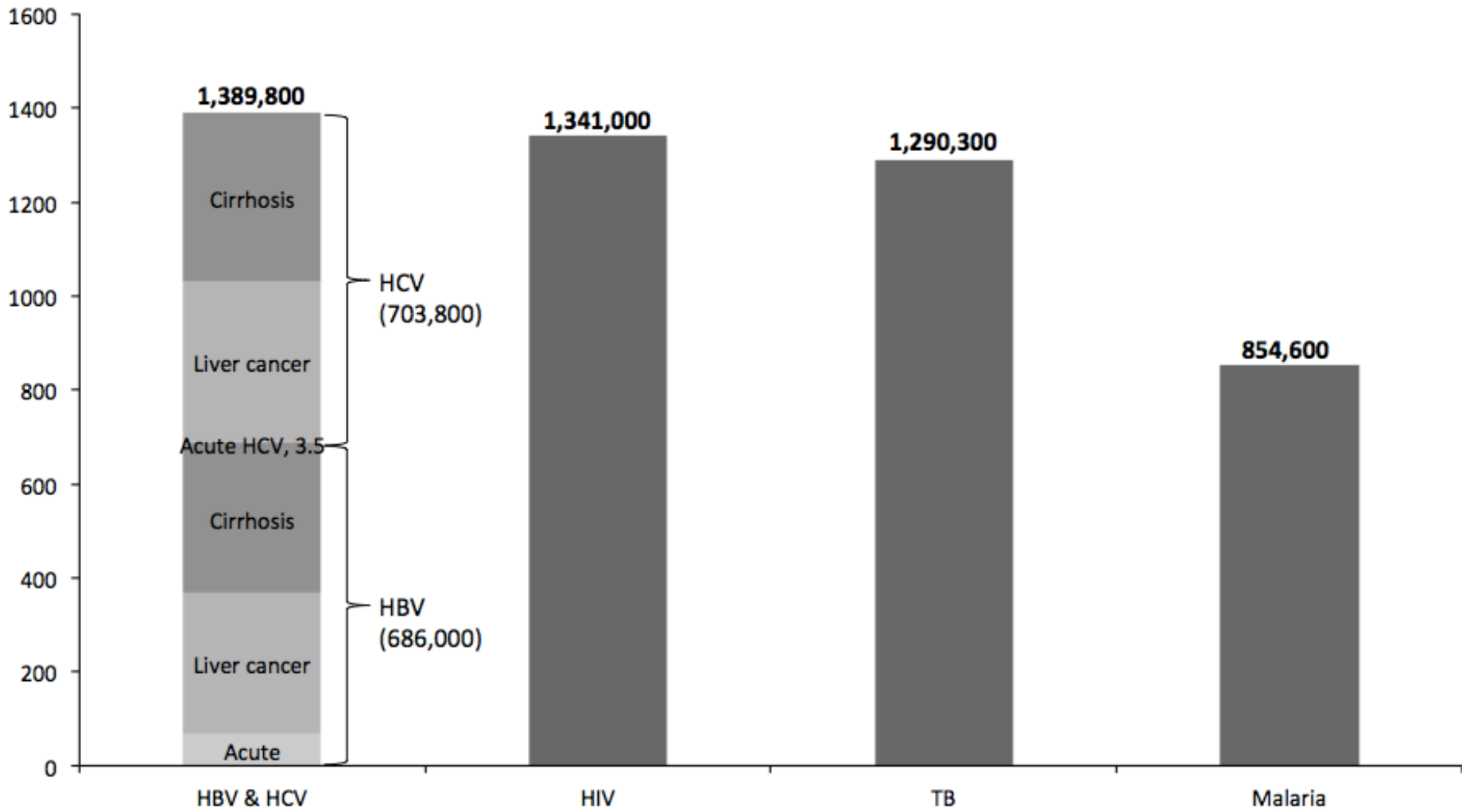
# Total deaths worldwide from HIV, Viral Hepatitis, TB and malaria, 1990-2013

Global Burden of Disease database.



Source: <http://ghdx.healthdata.org/global-burden-disease-study-2013-gbd-2013-data-downloads>

# Worldwide deaths from HCV, HBV, HIV, tuberculosis, and malaria in 2013



Treatment to cure HCV  
can be made cheaply

# HCV genotypes 1-6 worldwide

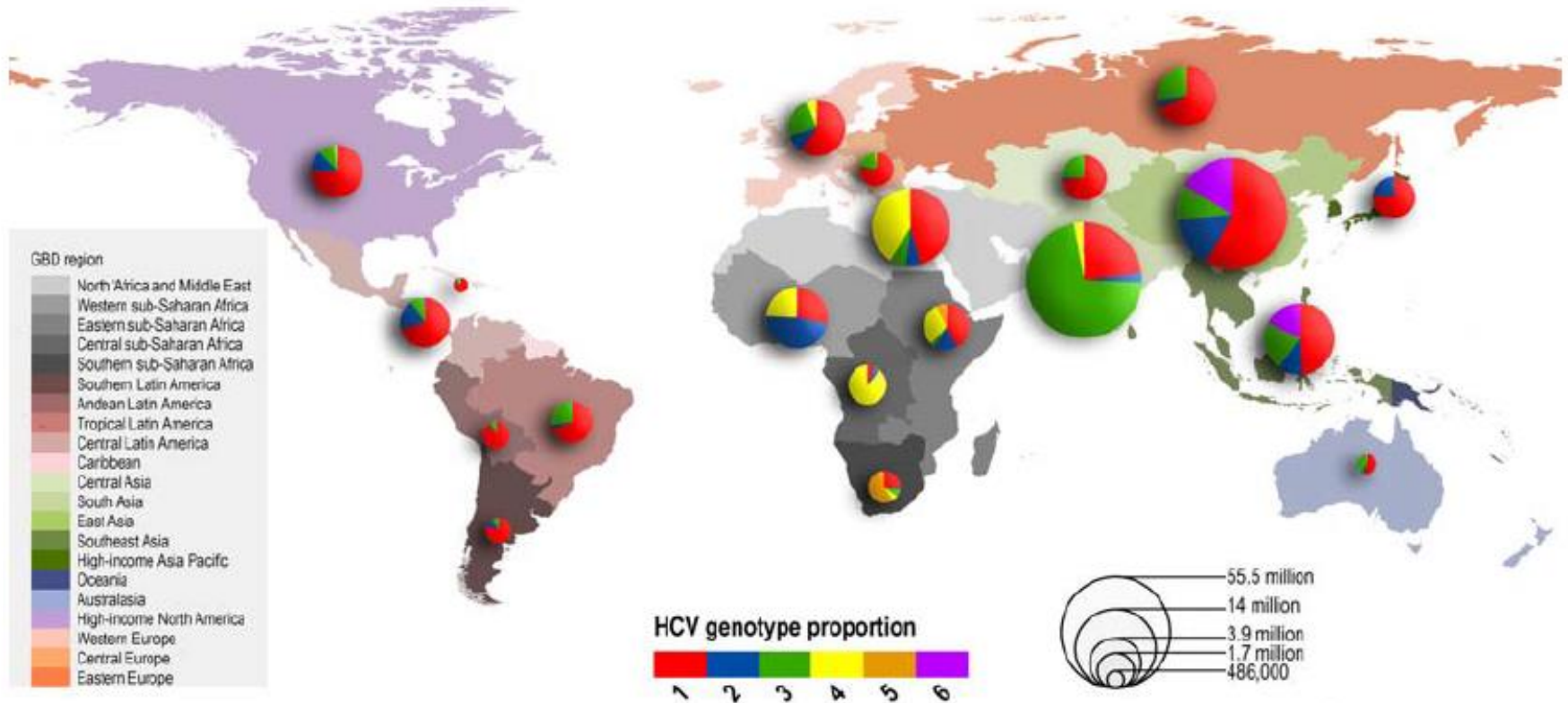
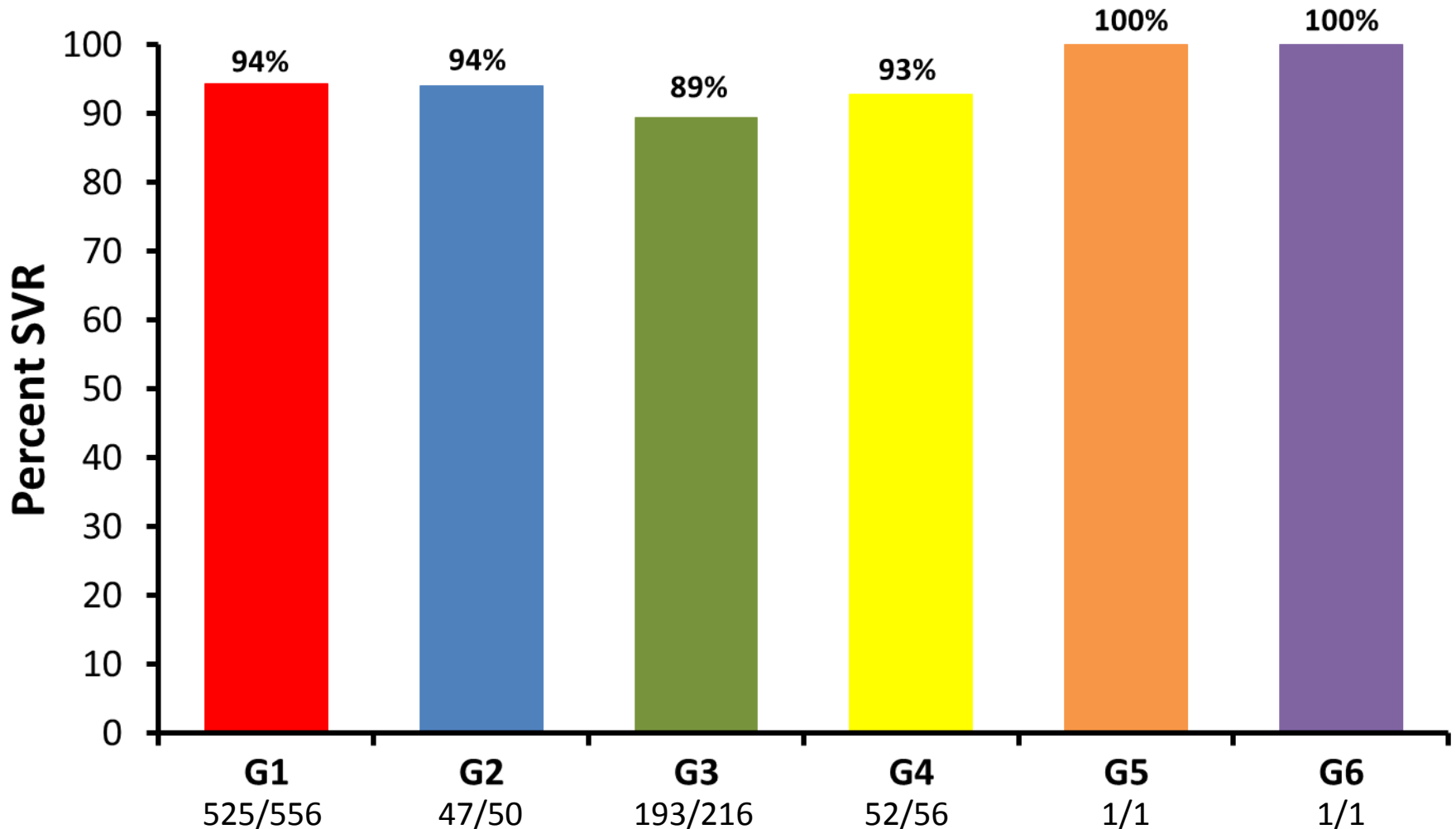


Fig. 1. Relative prevalence of each HCV genotype by GBD region. Size of pie charts is proportional to the number of seroprevalent cases

# Sofosbuvir + Daclatasvir ± RBV (12-24 wks)

## Percentage of people cured, by Genotype



Sources: A1444040 trial; ALLY-1; ALLY-2; ALLY-3; 3 French EAPs

# Estimating minimum costs of treatment

Tracking import-export databases to find costs of API (Active Pharmaceutical Ingredient – drug substance before formulation and packaging).

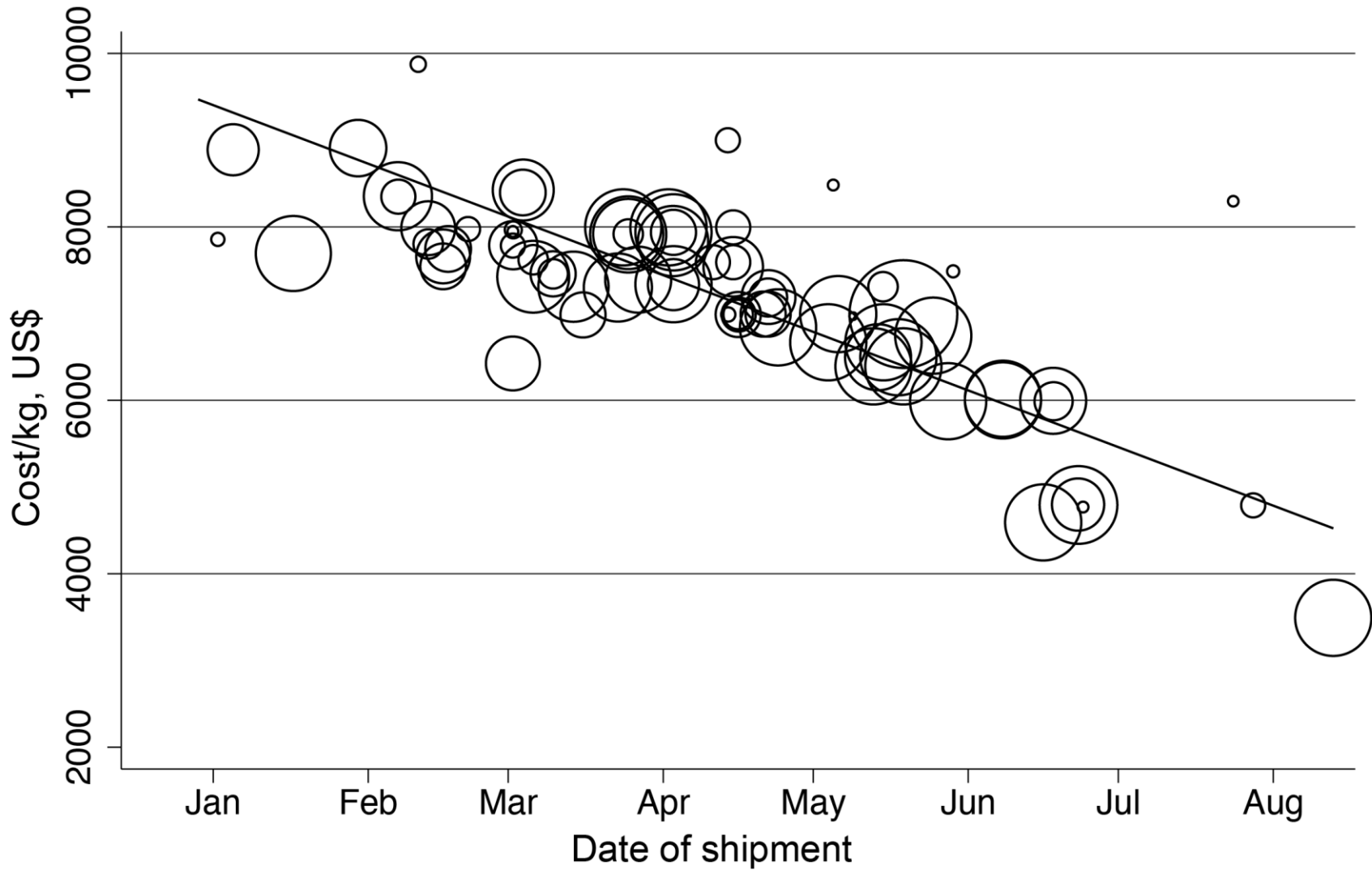
[www.indiainfodrive.com](http://www.indiainfodrive.com)

Then add costs of final formulation and profit margin using established methods.

Collaboration with experts in chemical synthesis and mass production of medicines to evaluate prices. Cross-checks using different methods.

Surveys of costs of drugs by country

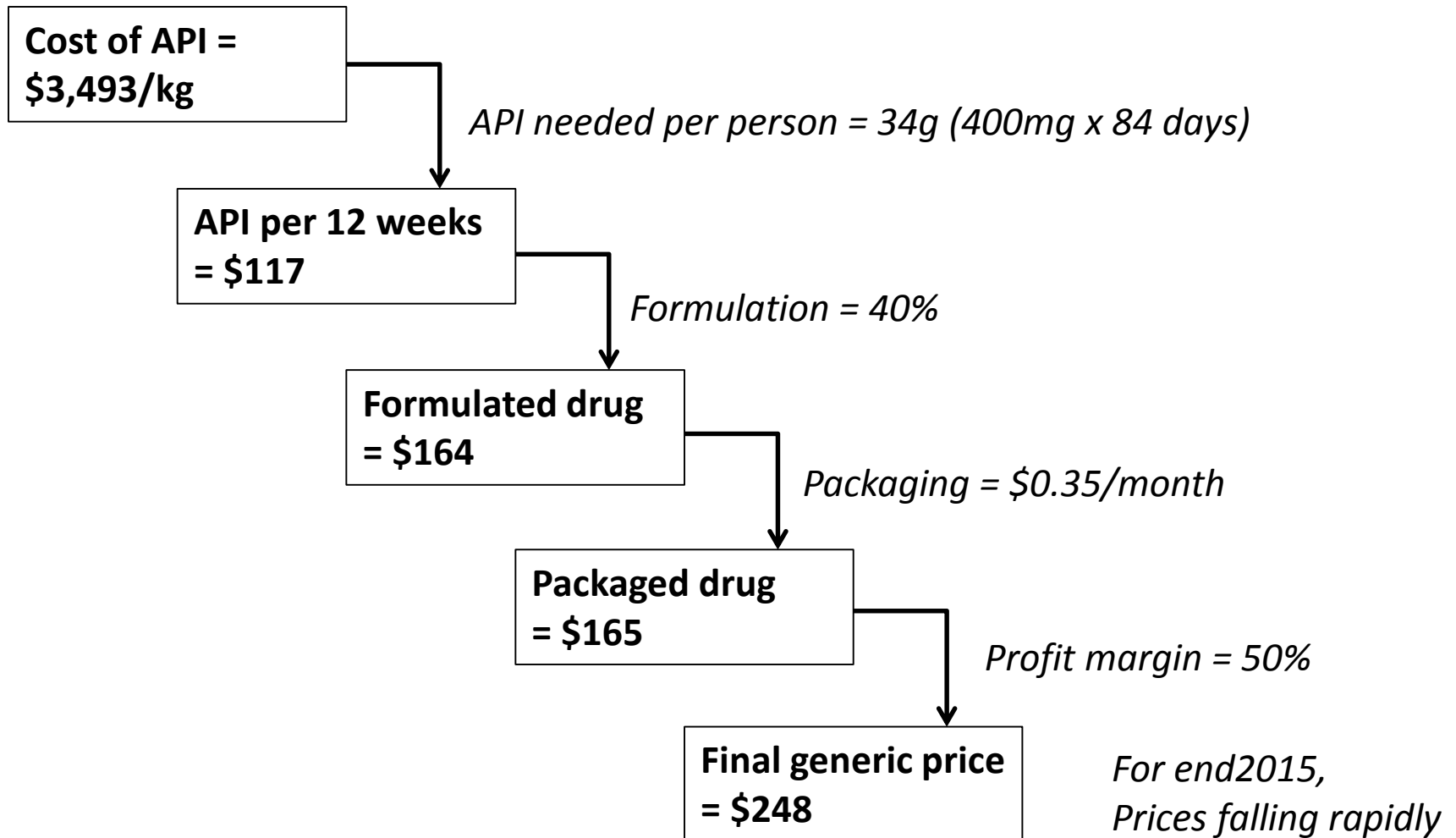
# Sofosbuvir API exported from India in 2015, weighted by size of shipment



○ 1kg  
○ 10kg  
○ 100kg



# Current Costs of production - sofosbuvir



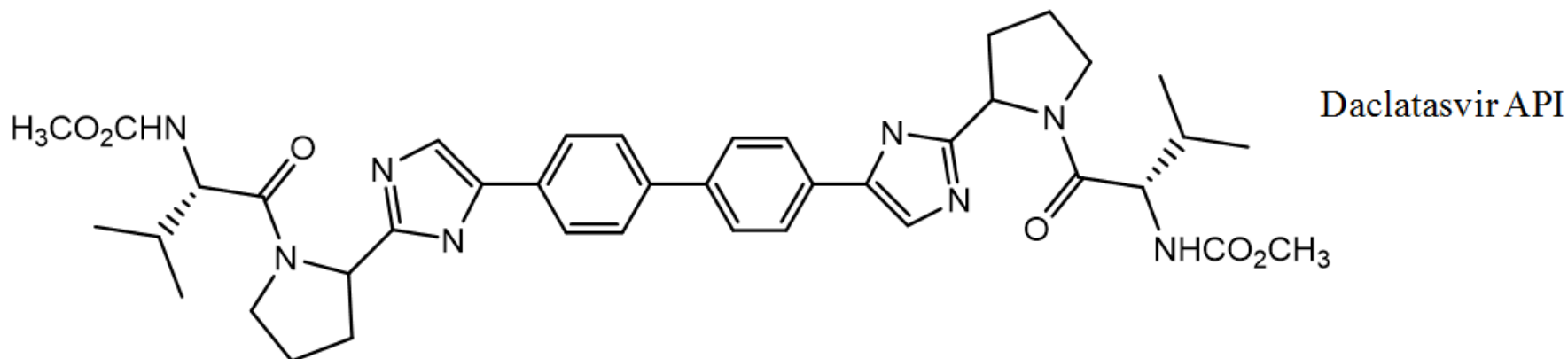
# Minimum cost to produce daclatasvir

**Chemical Formula:**  $C_{40}H_{50}N_8O_6$ . Molecular weight: 739g. NS5A inhibitor

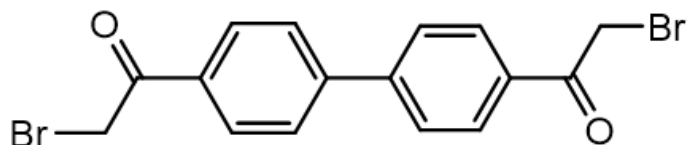
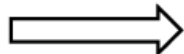
**Chemical synthesis:** straightforward synthesis given symmetry and availability of cheap starting materials to synthesize the side chains.

**Daily dose:** 60mg. 5 grams of drug required for 12 weeks of treatment (84 days)

**Estimated production cost:** \$4/gram (conservative). \$22 per 12 week course.

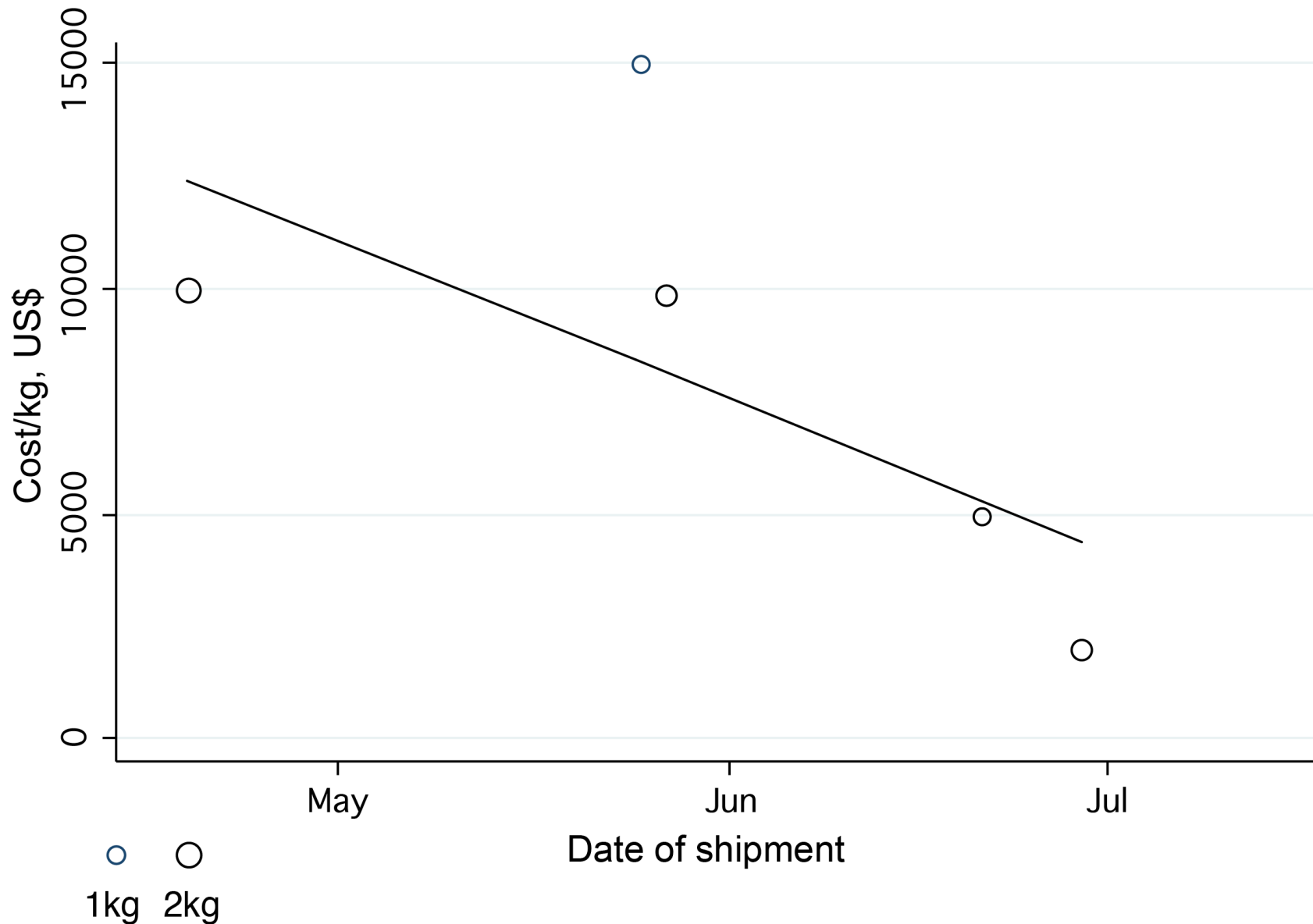


retrosynthesis

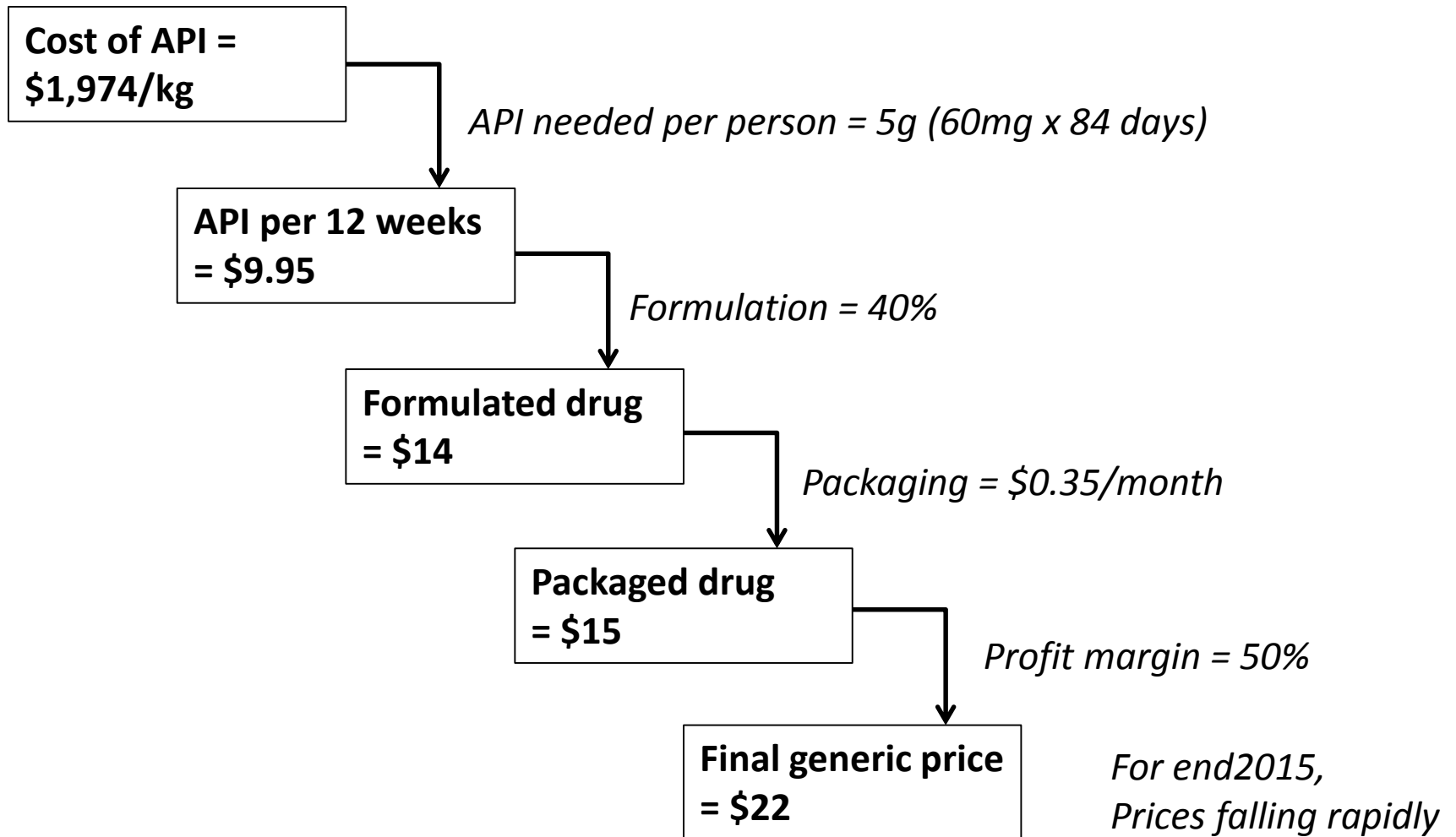


Cost-limiting raw material

# Daclatasvir API exported from India in 2015, weighted by size of shipment



# Current Costs of production - daclatasvir



**Entecavir for Hepatitis B  
one year's supply (0.18g)**

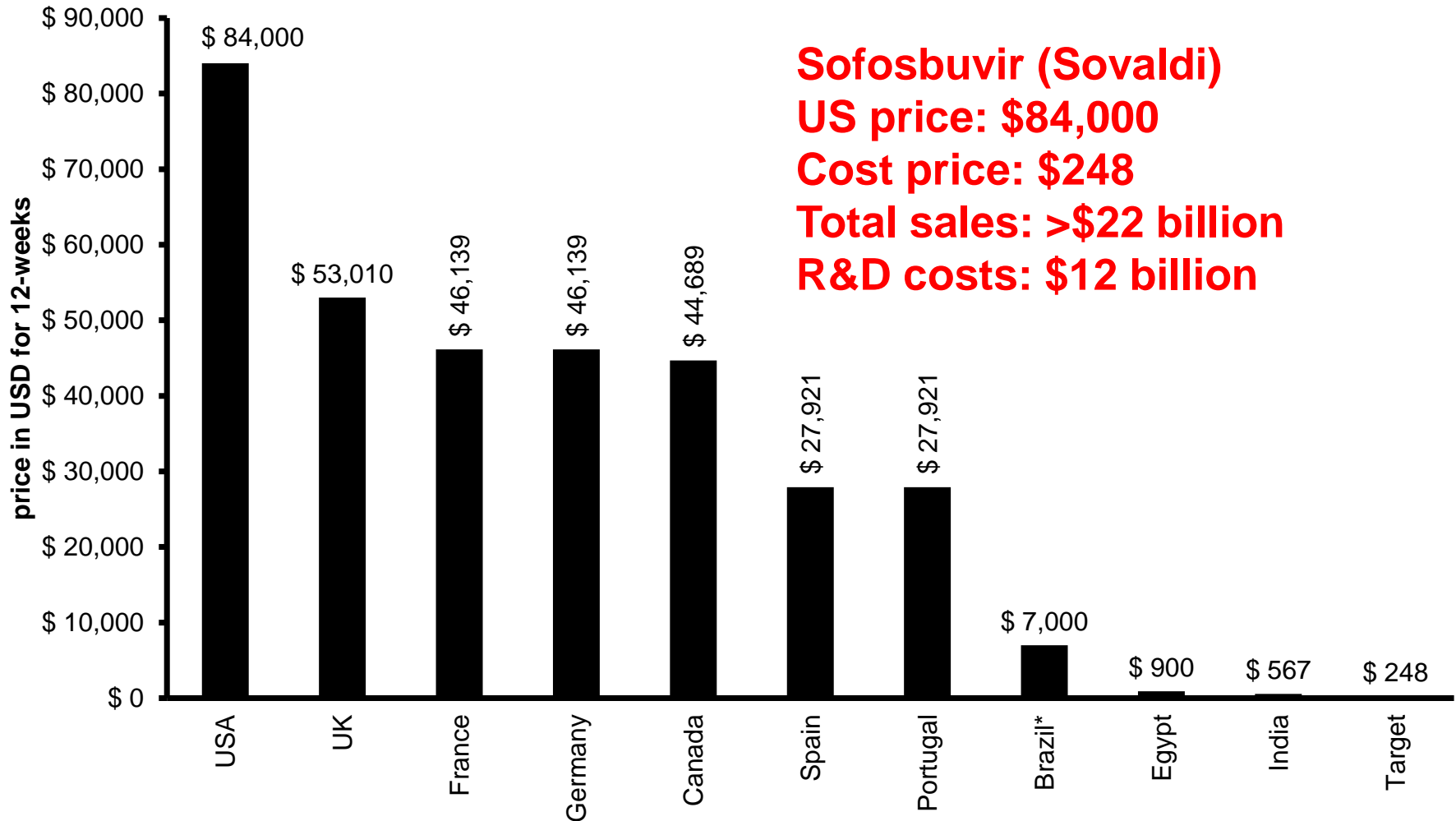


**Cost: \$36 / year**

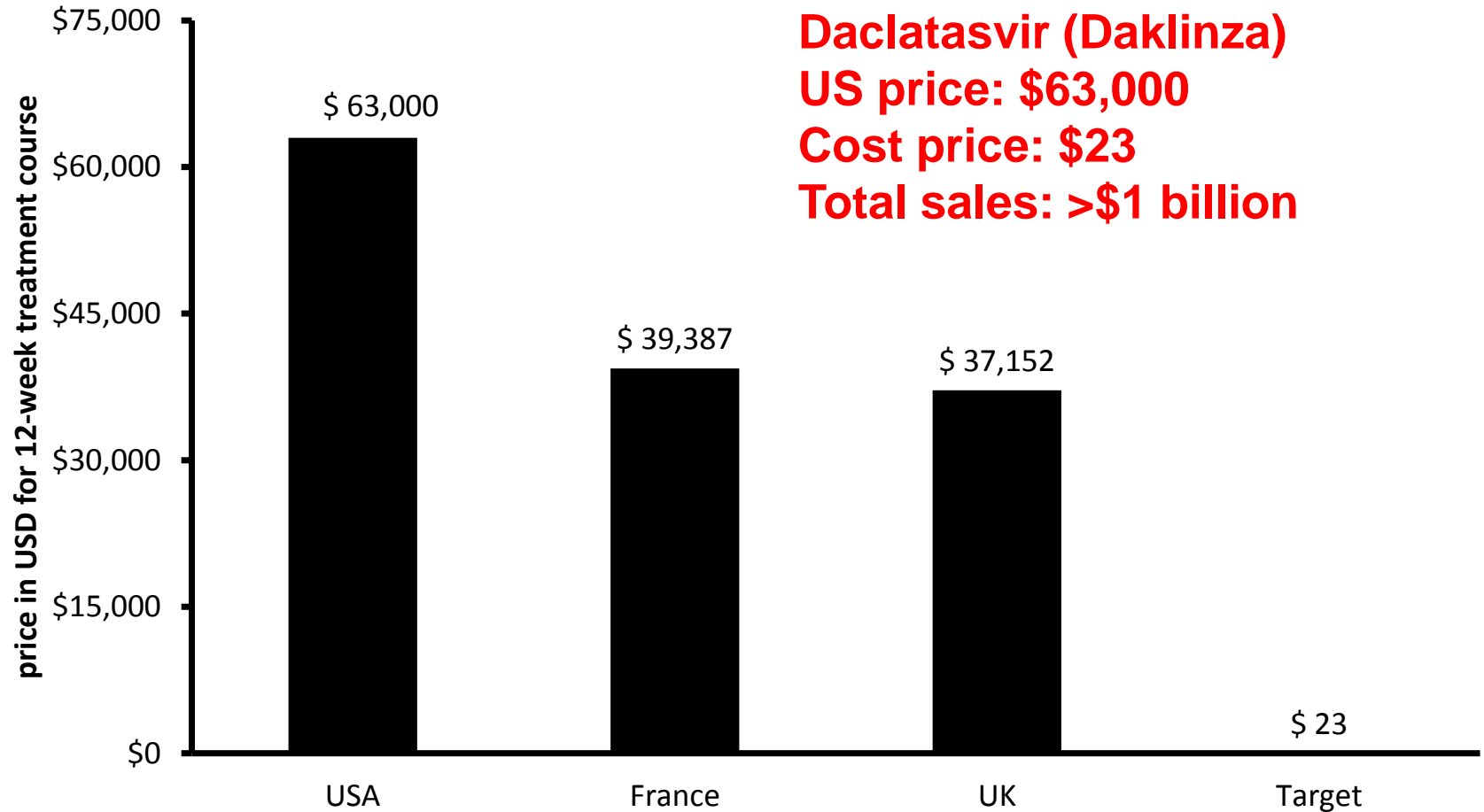
Treatments for HBV and HCV  
are sold for extremely high prices  
– this is restricting patient access

Gilead and BMS have already  
sold enough drugs to repay their  
costs of R&D

# Lowest prices of sofosbuvir by country (US dollars per 12 week course)



# Lowest prices of daclatasvir by country (US dollars per 12 week course)





## 5g of diamonds

25 1-carat (\$1900 each)

Cost = \$48,000



## 5g of daclatasvir

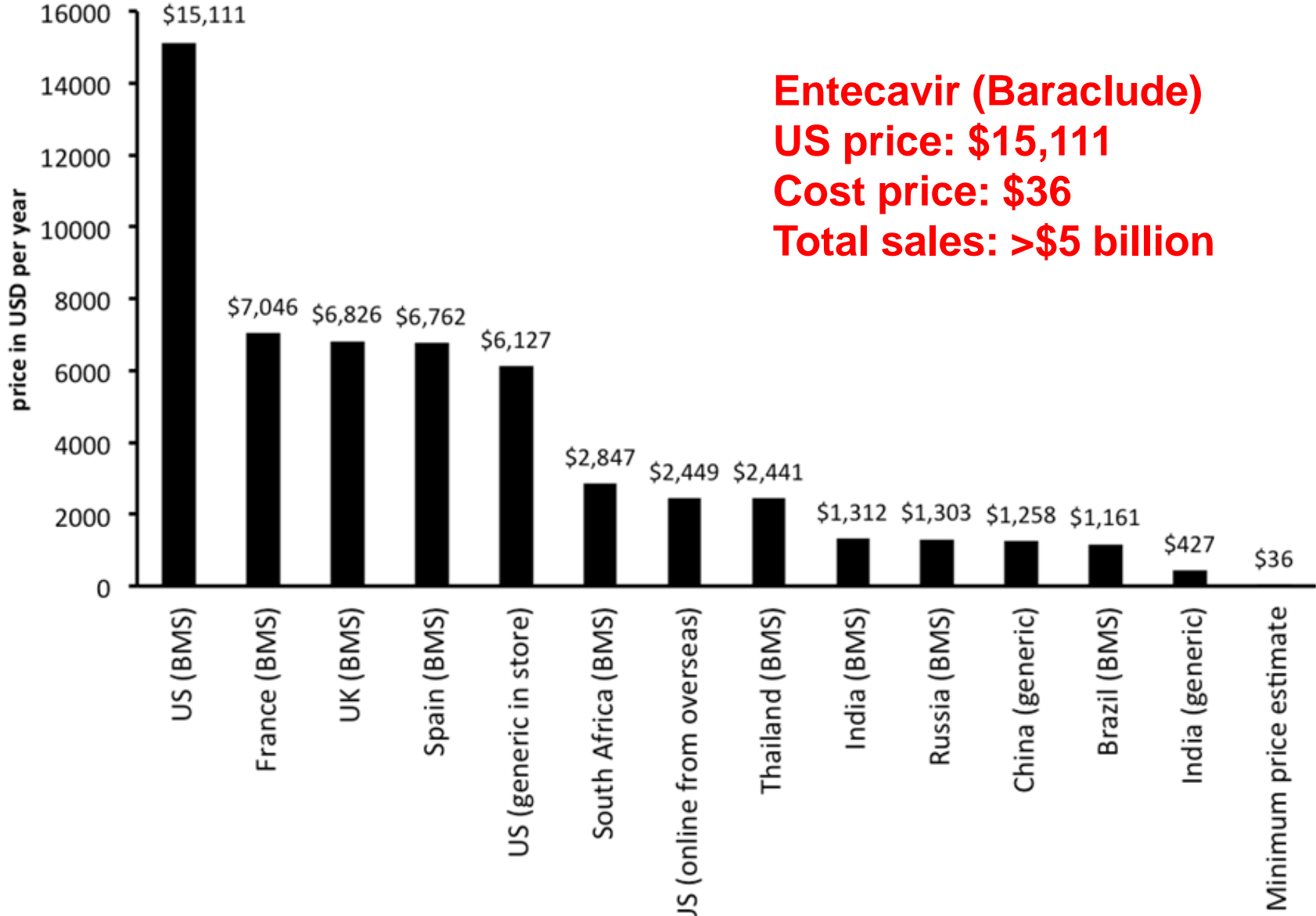
12 weeks of treatment, 60mg/day

Cost = \$63,000 (US price)



# Entecavir for Hepatitis B

## cost per person/year by country



**Entecavir (Baraclude)**  
**US price: \$15,111**  
**Cost price: \$36**  
**Total sales: >\$5 billion**

# Costs of drugs by country

Top 20 selling drugs worldwide (IMS 2014)

Analysis of minimum prices by country

Overall, drug prices in USA are 3 times higher than the UK

Drug prices in the USA are 16 times higher than in India

# Costs of top 20 drugs by country

---

Drug	Company	USA	UK	India
<b>Sofosbuvir / Sovaldi</b>	<b>Gilead</b>	<b>\$82,446</b>	<b>\$53,120</b>	<b>\$567</b>
Pegfiligastra (Neulasta)	Amgen	\$61,693	\$18,065	\$2373
Etanercept (Enbril)	Immunex	\$32,457	\$14,115	\$12,378
Glatiramer (Copaxone)	Sandoz	\$29,971	\$10,176	\$6862 (BR)
Aripiprezole (Ablify)	Otsuka	\$4509	\$1901	\$39
Insulin (Lantus)	Sanofi	\$4605	\$805	\$473
Insulin aspart (Novorapid)	Novo Nordisk	\$4143	\$549	\$433

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# Costs of top 20 drugs by country

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Drug	Company	USA	UK	India
Sitagliptin (Januvia)	Merck	\$3949	\$658	\$239
Pregabalin (Lyrica)	Sandoz	\$3767	\$1275	\$27
Tiotropium (Spiriva)	Boeringher Ing	\$3712	\$694	\$17
Fluticazone (Seratide)	GSK	\$3701	\$647	\$178
Budesonide (Symbicort)	AstraZeneca	\$3425	\$554	\$39
Rosuvastatin (Crestor)	IPR	\$2577	\$357	\$25

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# Costs of monoclonal antibodies

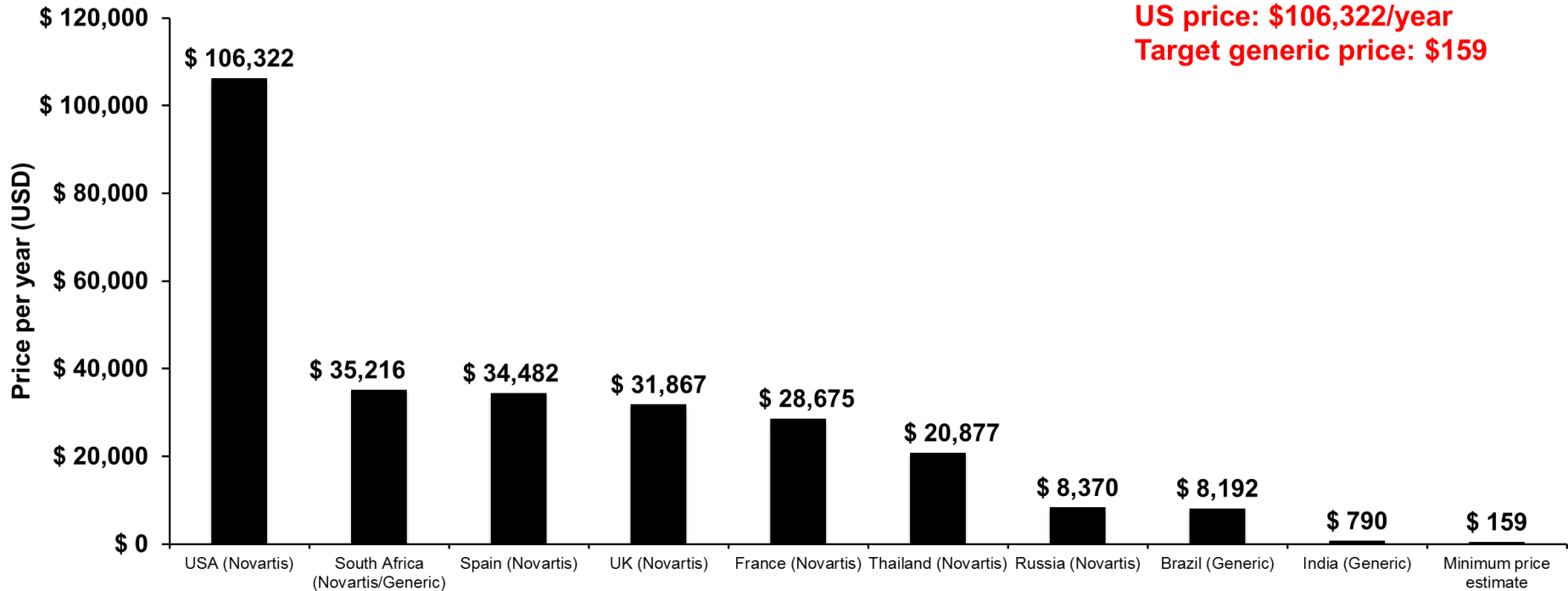
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Drug	Company	USA	UK	Brazil
Bevacizumab (Avastin)	Genetech	\$76,826	\$41,057	\$39,898
Trastuzumab (Herceptin)	Roche	\$51,426	\$19,301	\$10,780
Adalimumab (Humira)	AbbVie	\$36,447	\$13,902	\$5,396
Rituximab (MabThera)	Genentech	\$23,612	\$10,739	\$3,951
Infliximab (Remicade)	Centocor	\$8,693	\$7,455	\$2,792

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# Imatinib – for treatment of Leukaemia (CML and ALL)

Annual prices of Imatinib (400mg) in selected countries

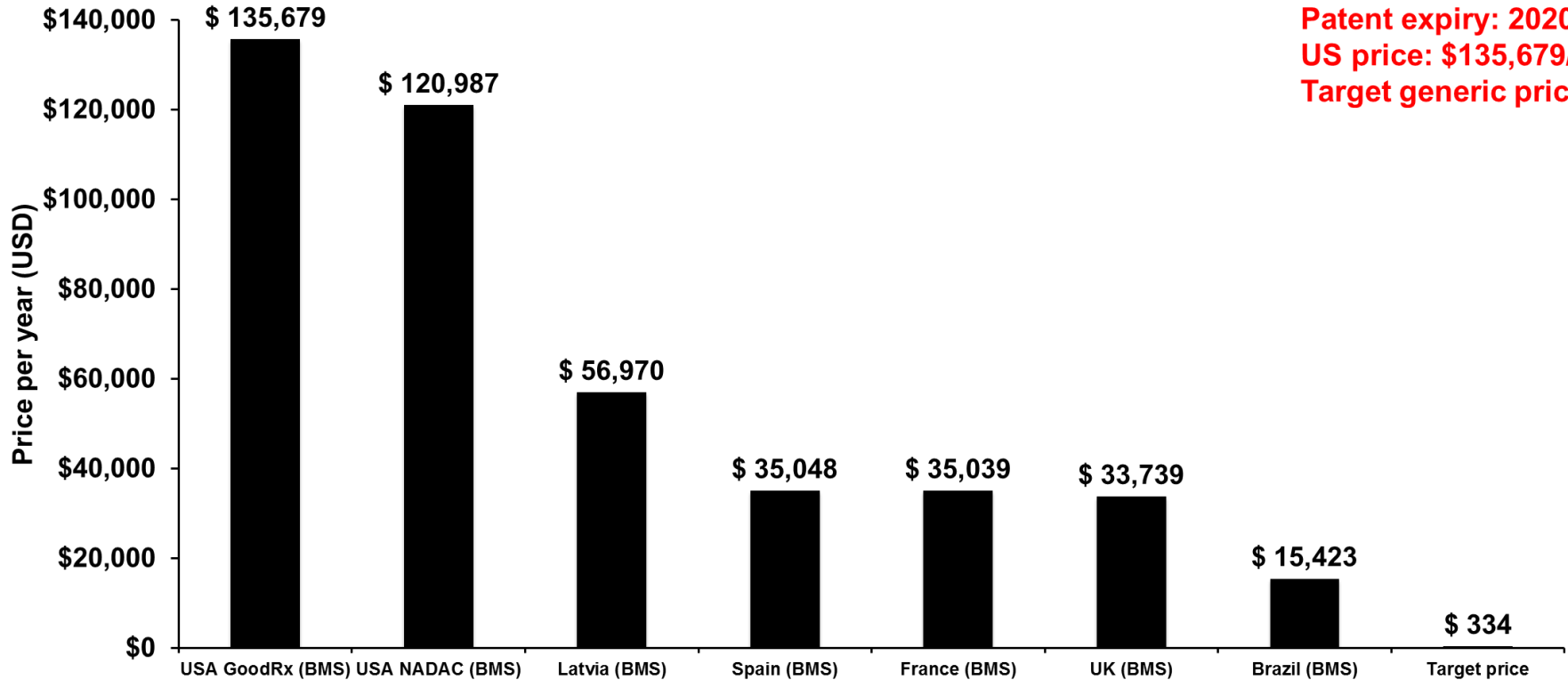


Presented at 18<sup>th</sup> ECCO - 40<sup>th</sup> ESMO European Cancer Congress,  
27<sup>th</sup> September 2015, Vienna, Austria [abstract number: 1203]

# Dasatinib – for treatment of leukaemia

Annual prices of Dasatinib (100mg) in selected countries

Dasatinib (Sprycel)  
Patent expiry: 2020  
US price: \$135,679/year  
Target generic price: \$334



Presented at 18<sup>th</sup> ECCO - 40<sup>th</sup> ESMO European Cancer Congress,  
27<sup>th</sup> September 2015, Vienna, Austria [abstract number: 1203]



SVR leads to clinical benefits and  
improved survival

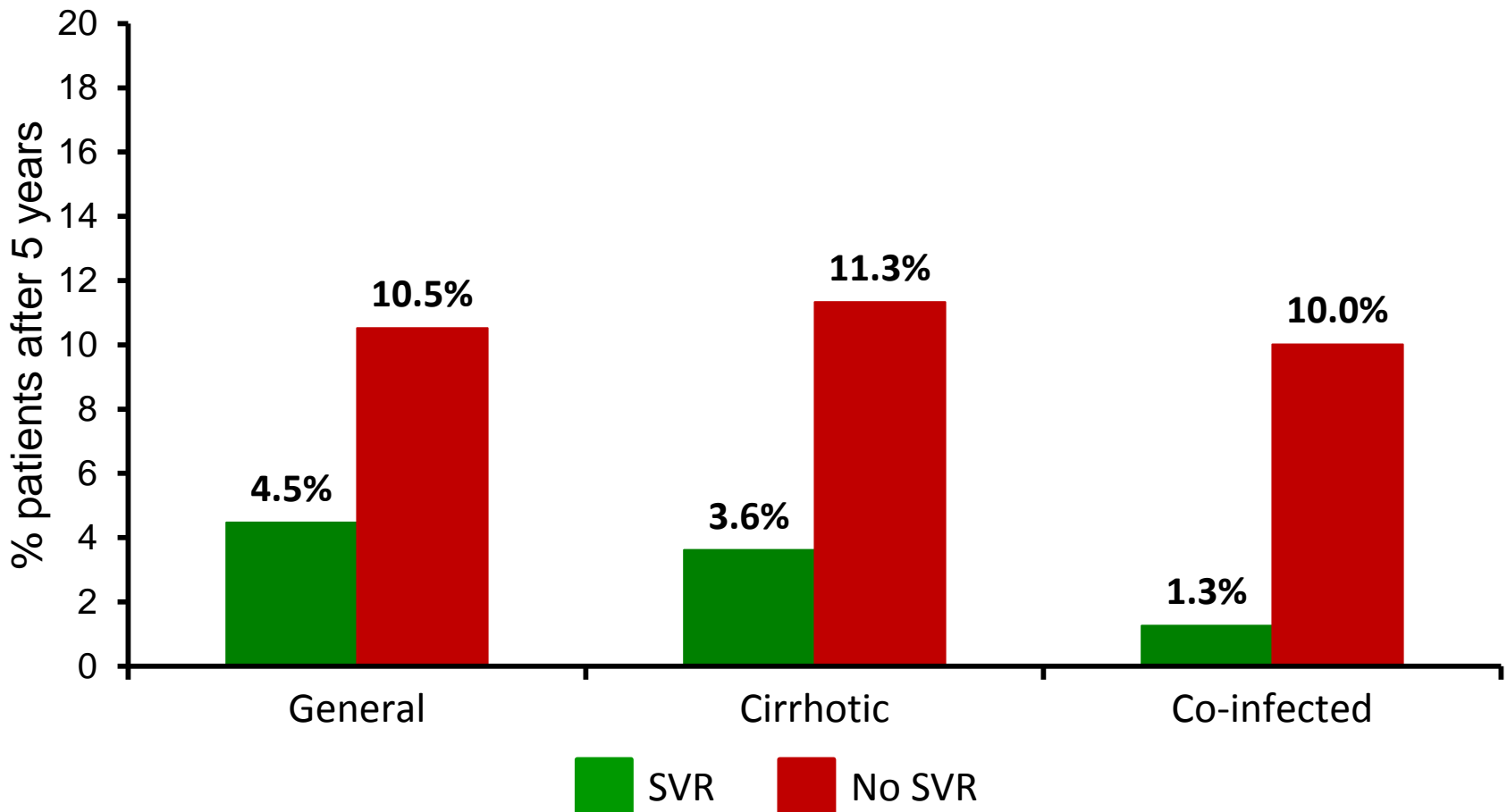
However, re-infection reverses  
these benefits

# Five year outcomes: deaths (all-cause)

**General: 18 studies**  
n=29,269  
Avg. FU=4.6 years

**Cirrhotic: 9 studies**  
n=2,734  
Avg. FU=6.6 years

**HIV/HCV: 5 studies**  
n=2,560  
Avg. FU=5.1 years

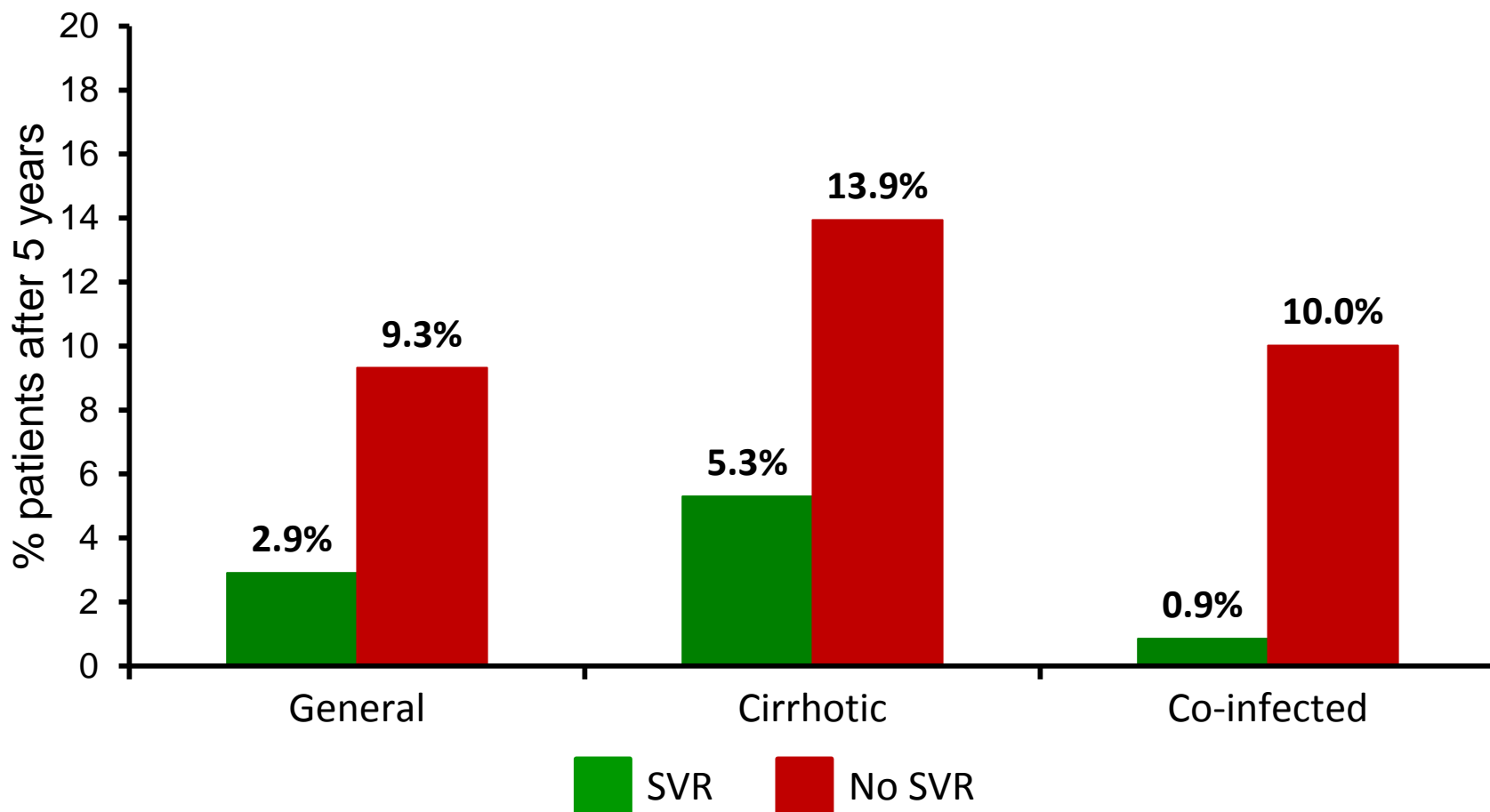


# Five year outcomes: Hepatocellular carcinoma (HCC)

**General: 21 studies**  
n=12,496  
Avg. FU=6.1 years

**Cirrhotic: 18 studies**  
n=4,987  
Avg. FU=6.6 years

**HIV/HCV: 3 studies**  
n=2,085  
Avg. FU=4.7 years

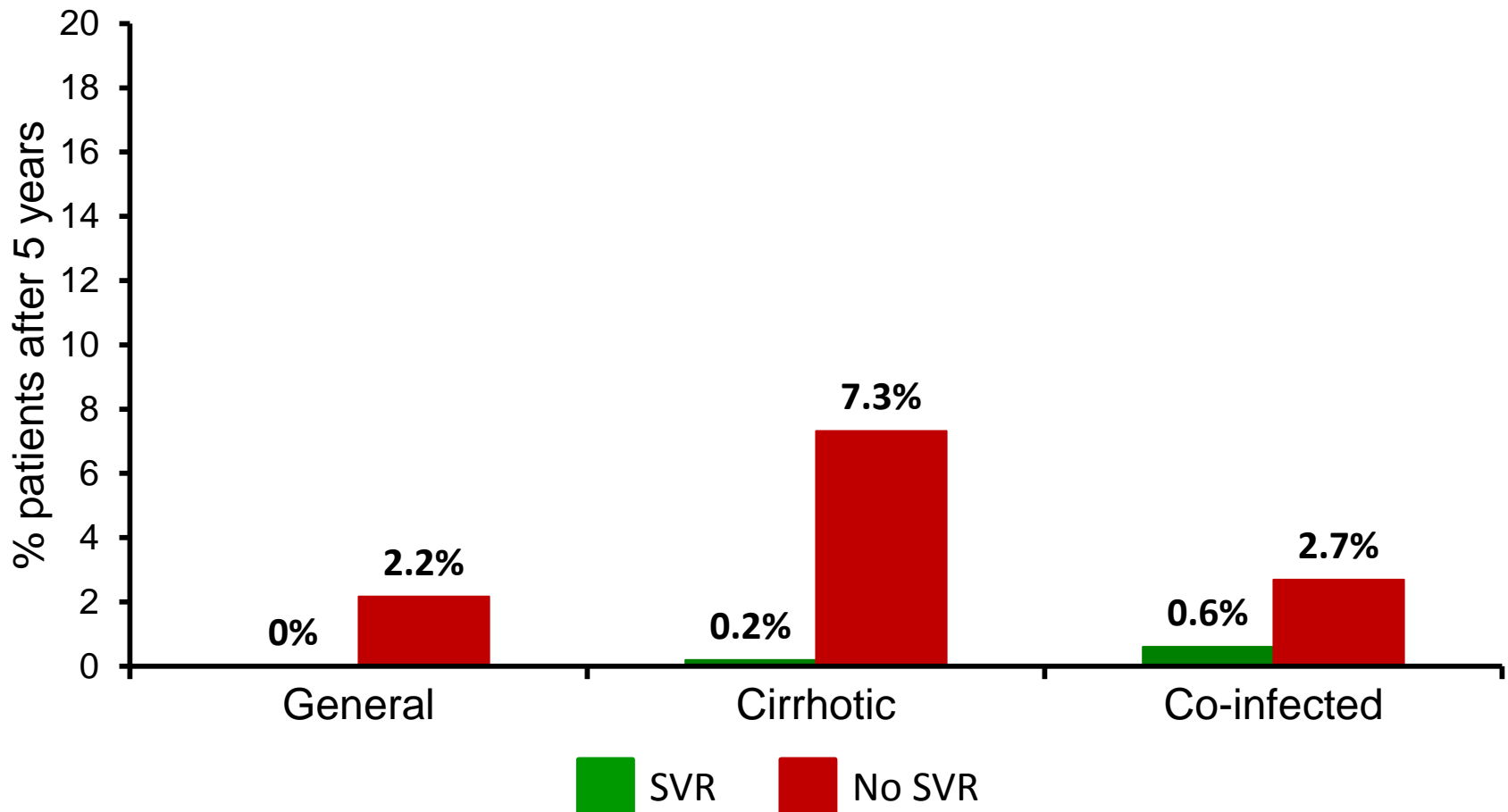


# Liver transplantation after 5 years

**General: 1 study**  
n=108  
Avg. FU=4.2 years

**Cirrhotic: 2 studies**  
n=1,046  
Avg. FU=7.7 years

**HIV/HCV: 2 studies**  
n=2,039  
Avg. FU=4.9 years



# Five year risk of HCV re-infection post-SVR

## Low-risk

24 studies

n=6,046

Avg. FU=4.1 years

## IVDU / prisoners

16 studies

n=1,203

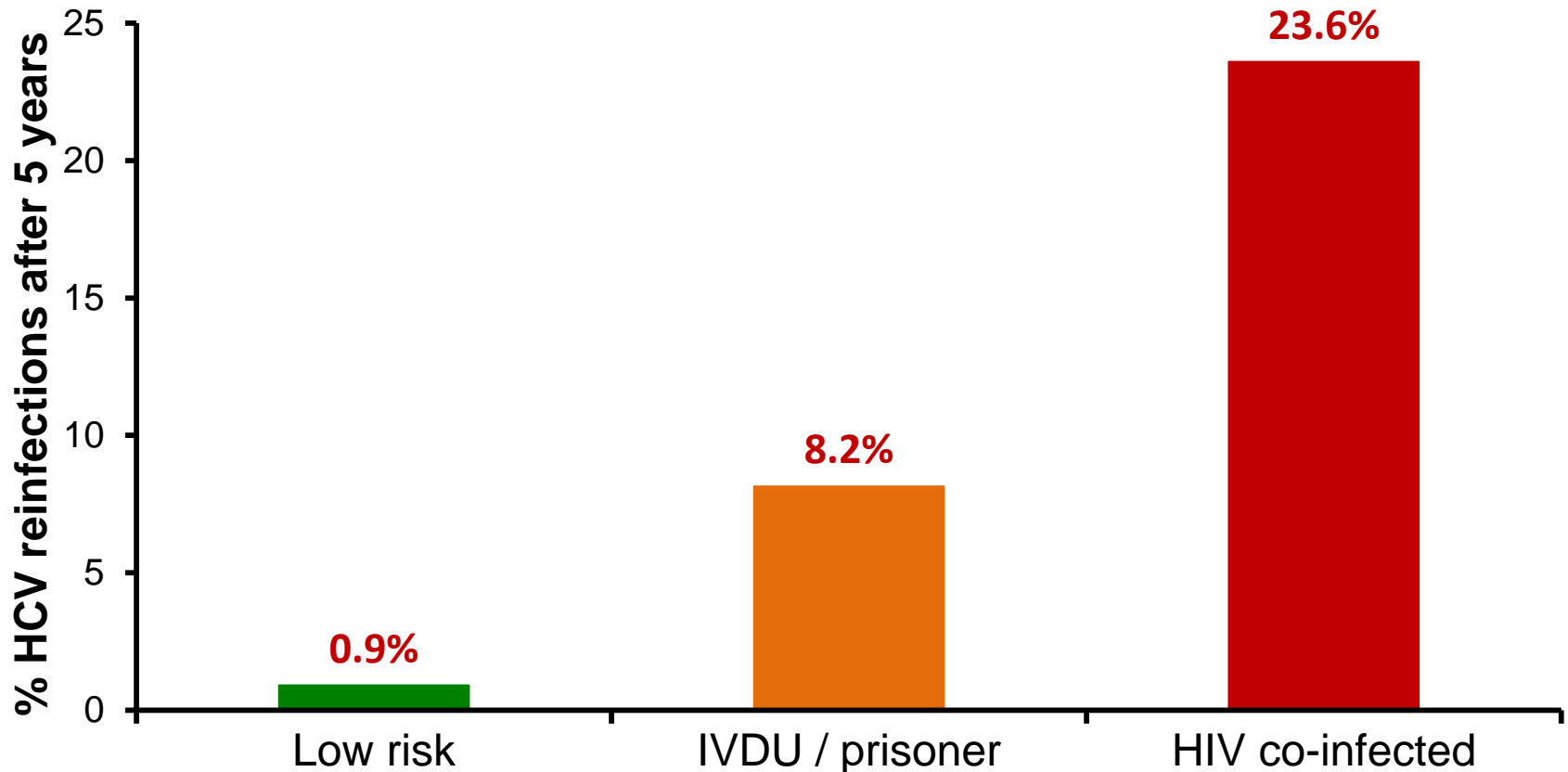
Avg. FU=5.0 years

## HIV co-infected

10 studies

n=1,106

Avg. FU=3.1 years



Is it actually cost-effective to treat  
HCV at these extremely high  
prices?

# Budget impact

- Cost of treatment is so high that most national health budgets cannot afford to treat more than 5% of HCV infected people per year
- This limits the benefits of treatment in terms of lowering onward transmission – coverage is very limited.

# Re-infections

- The main cost-effectiveness models from Gilead, used for NICE evaluation, do not assume any re-infection.
- Post-SVR, 23.6% of HIV co-infected people are re-infected with HCV within 5 years. In a lifetime time horizon, this would mean almost everyone was re-infected.
- The UK record is 9 cures and re-infections – where is the value?
- In HIV, despite 70% of people on ART treatment in UK and Australia, the number of new HIV infections has not fallen – behavioural disinhibition.



# Lifetime time horizons

- Sofosbuvir is NOT cost-effective over standard of care within a 5-10 year time horizon
- Only cost-effective in a lifetime, but in the long-term, costs of treatment will fall (competition, generic approval).
- What is the benefit of treating F0-F2 patients now, if costs are set to fall significantly?

# Opportunity costs

- Why not spend the same money to treat people with HIV, TB or malaria?
- Cost of one HCV cure - \$1000 – is enough to treat someone with HIV for 10 years. Treating HIV would have a much higher survival benefit.
- HCV cost per cure needs to equal HIV cost per year of treatment to be of equal benefit – we are not at this stage.

# Conclusions

- Costs of HCV treatment are so high that elimination of this disease is unlikely before patent expiry.
- However, DAAs are extremely cheap to manufacture
- Pharmaceutical companies need to agree to treat more people for lower unit prices – would still make large profits

# Implications

- If agreement with pharmaceutical companies cannot be reached, other measures will be necessary, as for HIV:
  - Rejection of patents
  - Mass generic production in non-TRIPS countries
  - Health tourism
  - Buyers Clubs