The minimum cost to cure Hepatitis C - revisited

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International AIDS Society, Vancouver, Canada

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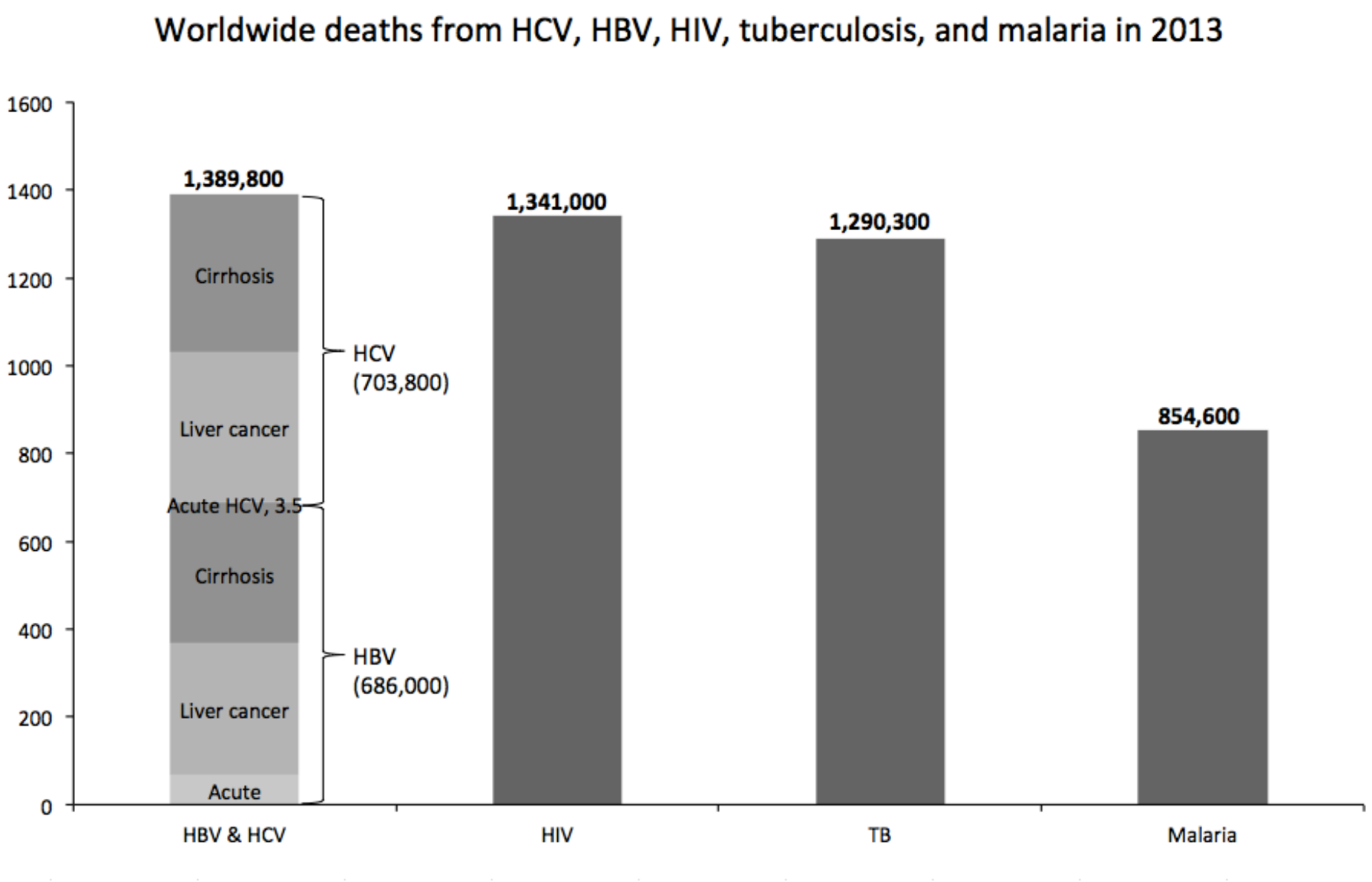
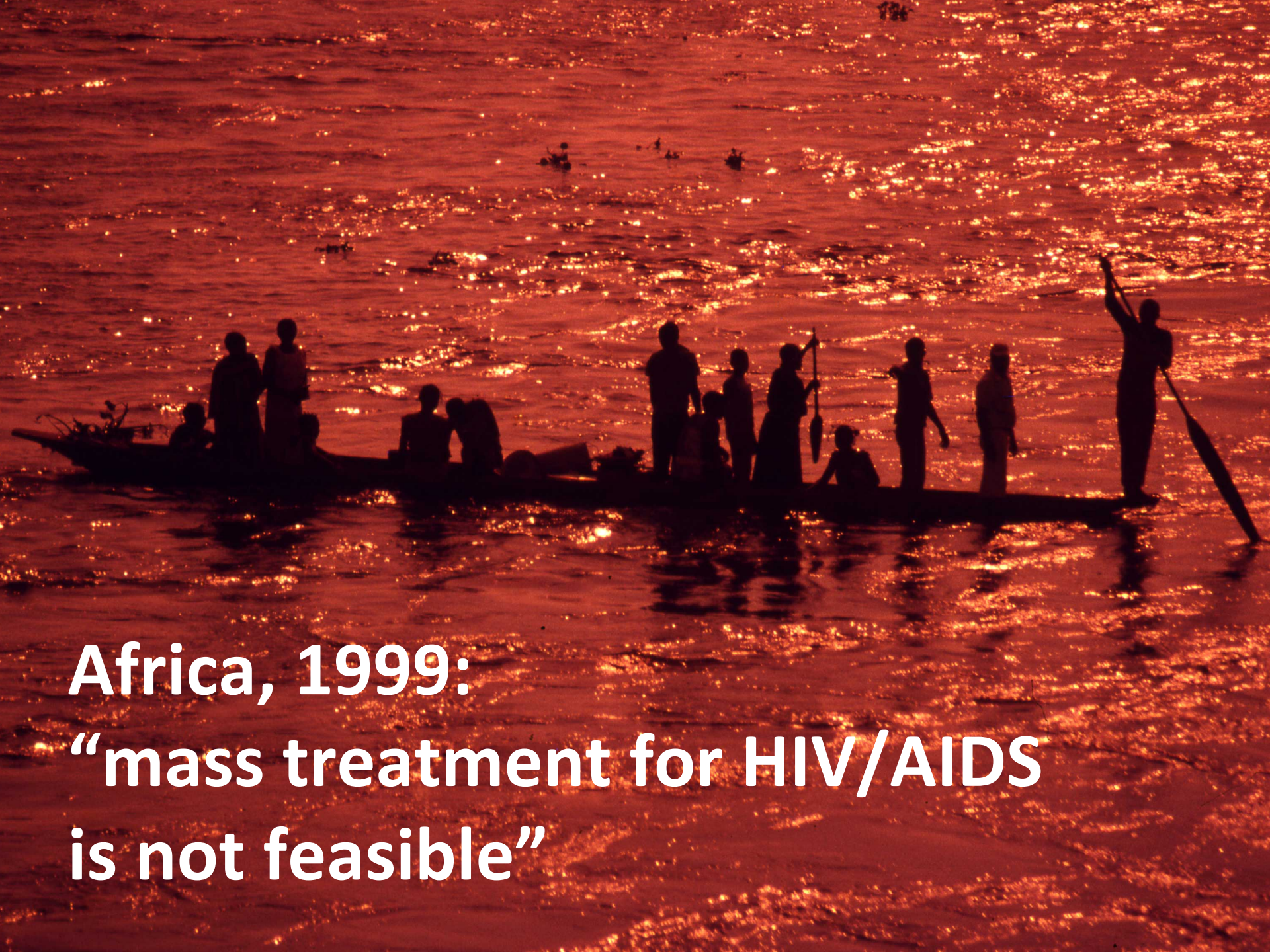


Global Burden of Disease report, Lancet 2014, 385: 117-171


Africa, 1999:
“mass treatment for HIV/AIDS
is not feasible”

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

Rationale

Generic antiretrovirals are currently manufactured at very low cost, for treatment of 15 million people with HIV/AIDS in low and middle-income countries.

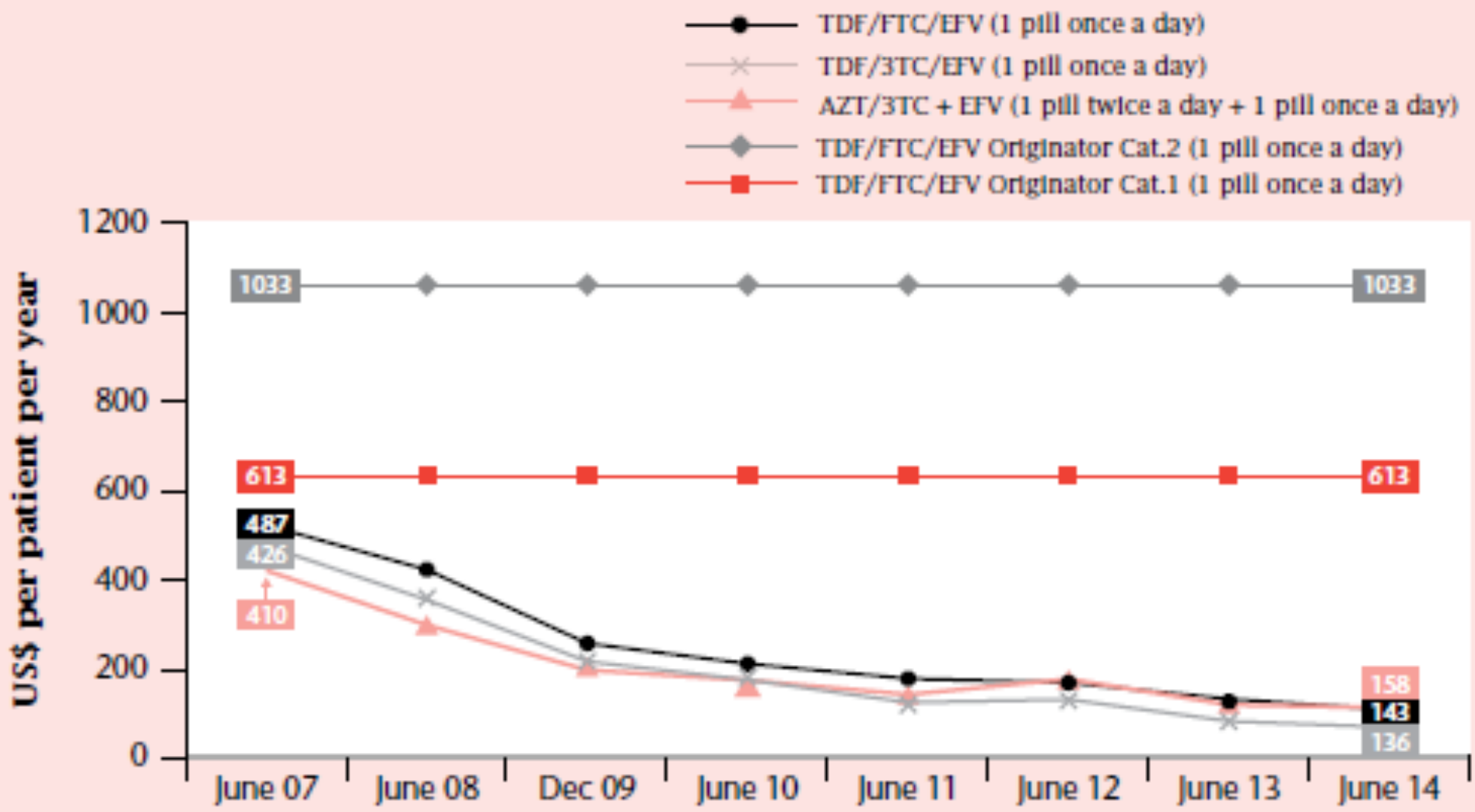
The cost of treating HIV in developing countries has fallen from over $10,000 per person/year in 2000, to under $136 per person in 2014.

Direct Acting Antivirals (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 courses of antiviral treatment available at very low cost.

Using the cost of mass-produced HIV drugs as a framework, we can make estimates for the potential minimum costs of HCV DAAs.

Price reductions for ARVs: 2007-2015



HIV Nucleos(t)ide inhibitors – production costs

Agent	Chemical formula	Molecular weight	Cost per kg ($)
abacavir	$C_{14}H_{18}N_6O$	286	**$650**
emtricitabine	$C_8H_{10}FN_3O_3S$	247	**$330**
stavudine	$C_{10}H_{12}N_2O_4$	224	**$860**
zidovudine	$C_{10}H_{13}N_5O_4$	267	**$260**
lamivudine	$C_8H_{11}N_3O_3S$	229	**$160**
tenofovir	$C_{23}H_{34}N_5O_{14}P$	636	**$240**

Source: Médecins Sans Frontières. Untangling the web of antiretroviral price reductions. 17th Edition – July 2014. http://utw.msfaccess.org/

Assumptions

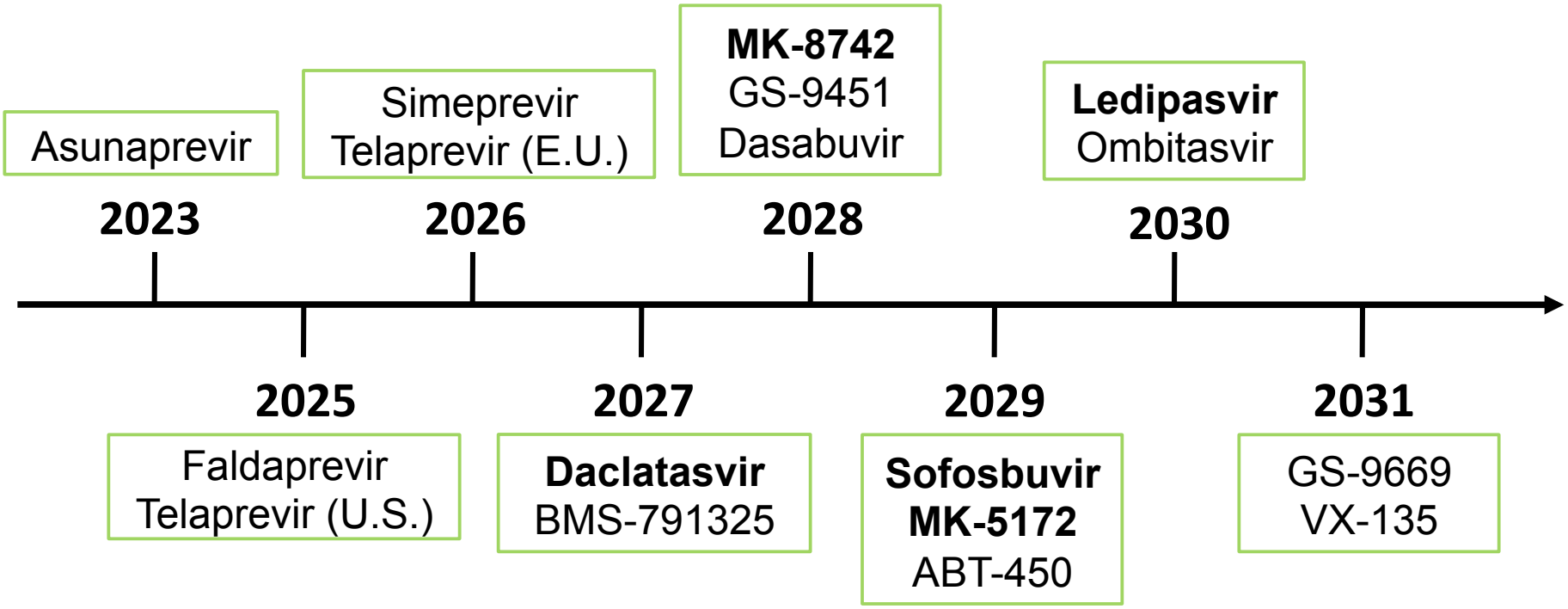
1. The same methods of generic manufacturing used to supply antiretrovirals to people with HIV/AIDS in developing countries.

2. No patent restrictions on mass drug production

3. Procurement of large orders for drug manufacture by generic companies (1-5 million people treated per year) in a competitive price market.

4. Use of minimal diagnostics to confirm HCV infection and then cure after treatment, plus safety monitoring

Patent Expiry Dates of HCV DAAs

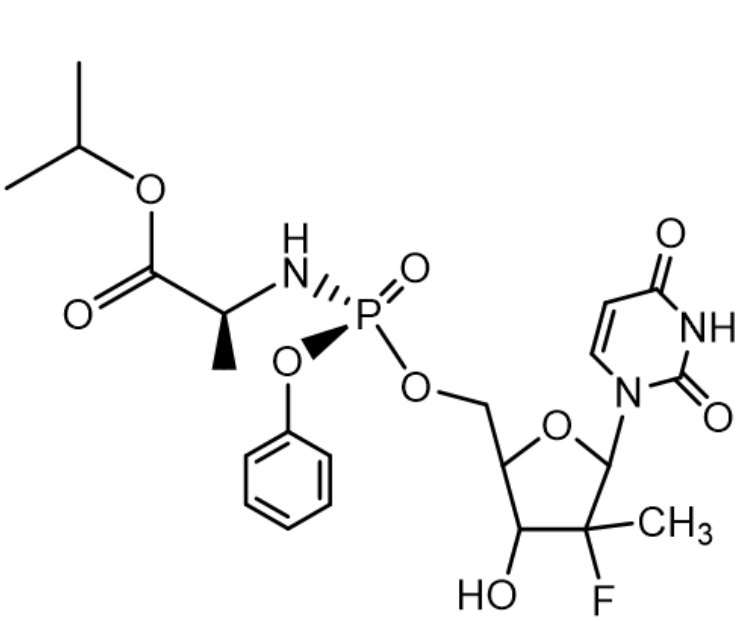


Calculation of treatment costs

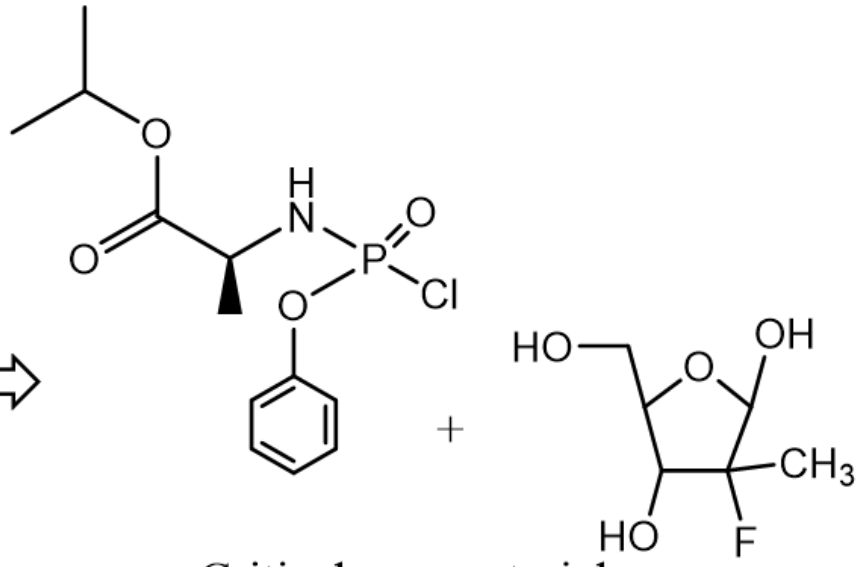
For each selected DAA, costs of mass production were estimated from:

- Known costs of API (active product ingredient)
- Daily dose (to calculate total API required)
- Treatment duration
- 40% margin for formulation.
- Cost of packaging
- 50% additional profit margin to generic suppliers

Cost for production of sofosbuvir

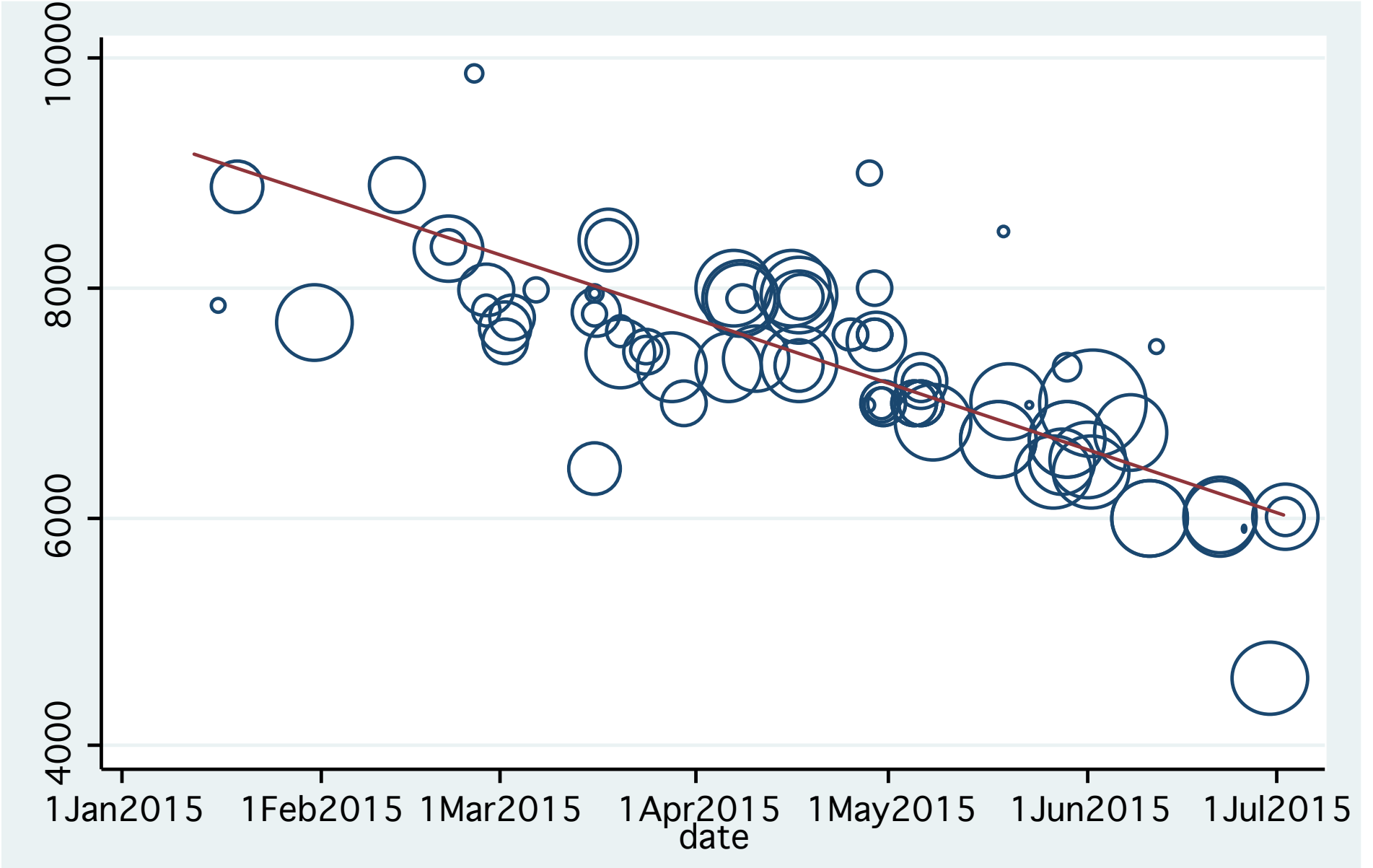


Sofosbuvir

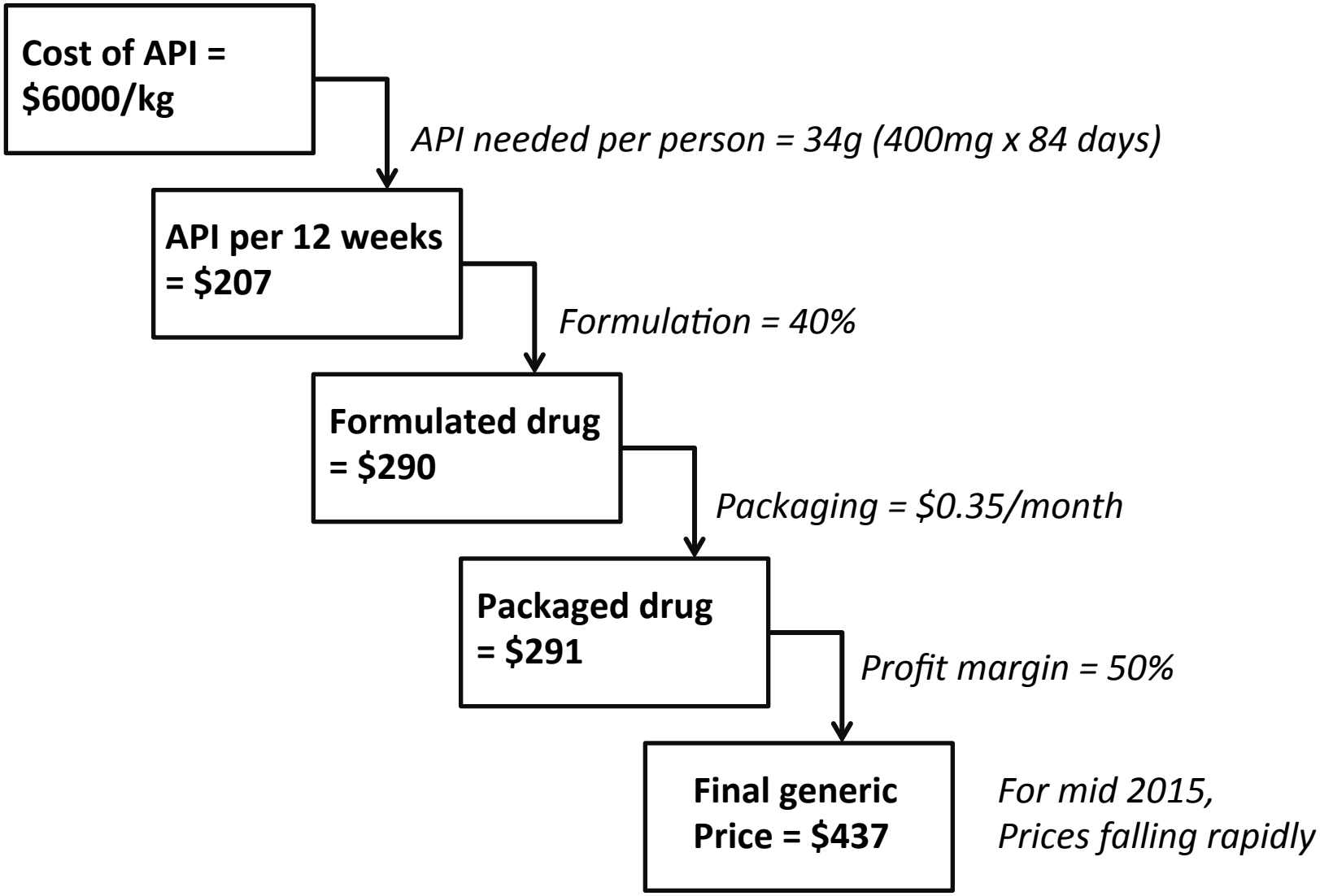


Critical raw materials

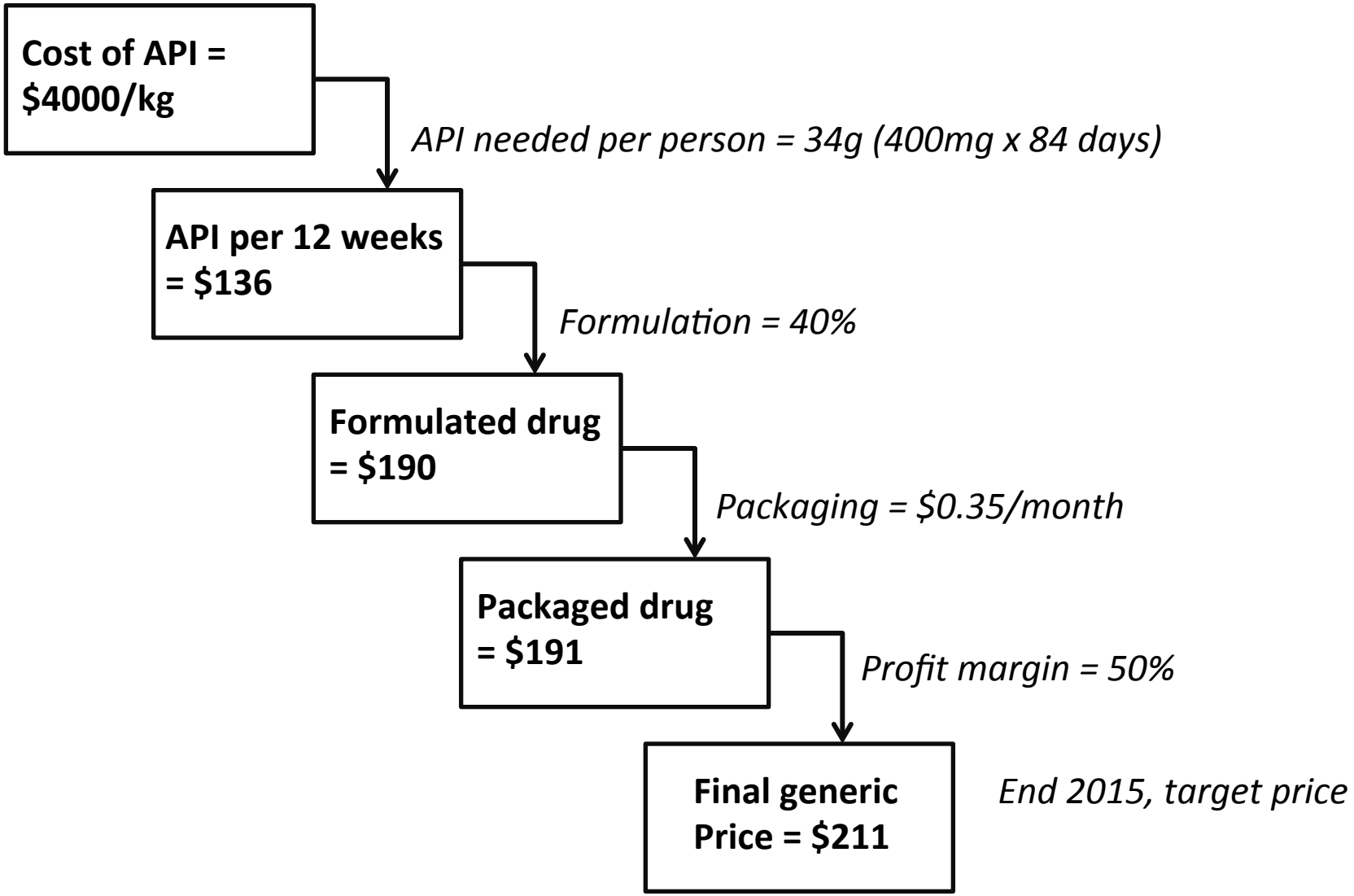
Exports of sofosbuvir (total 3500 kg) from Indian generic companies: cost/kg



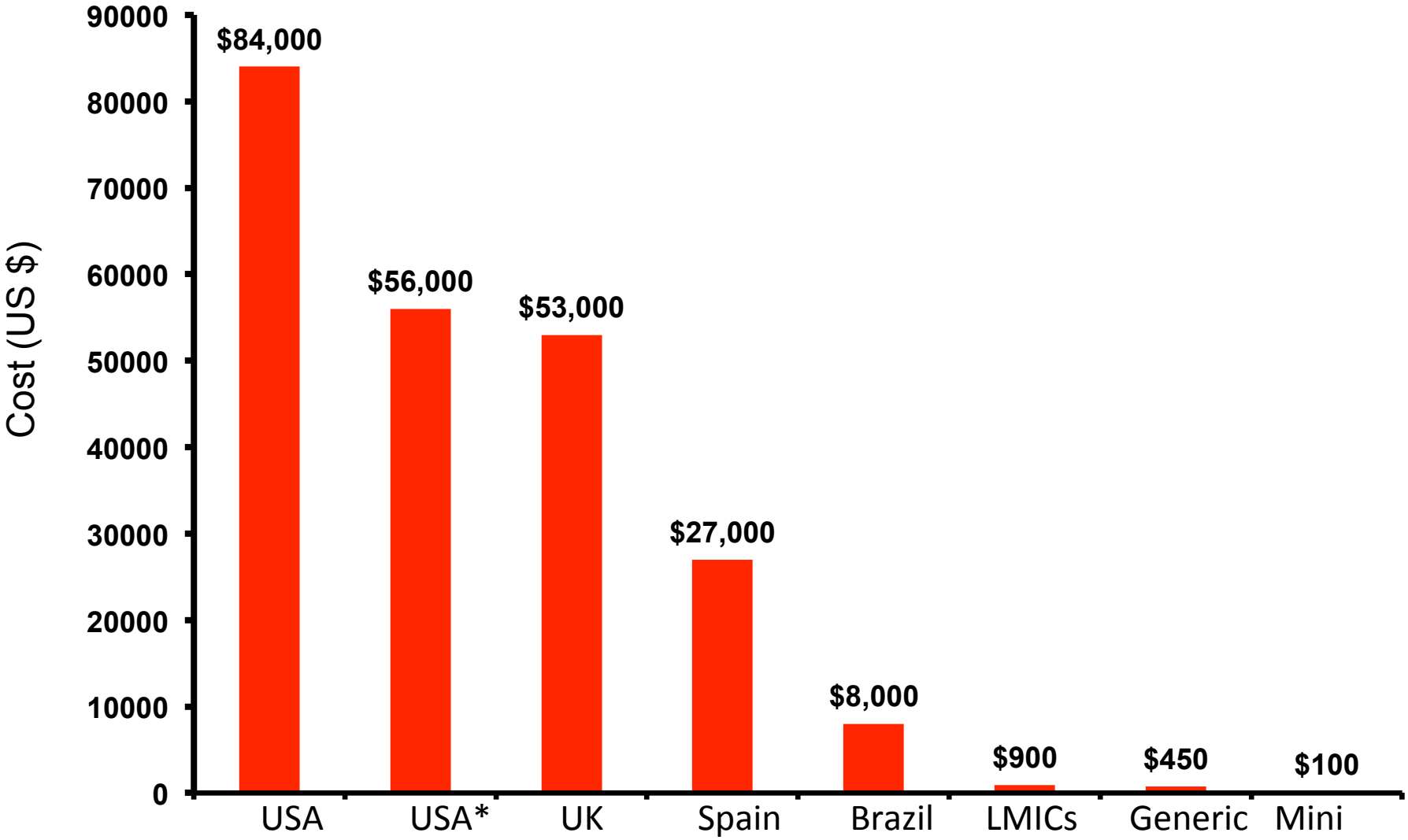
Sofosbuvir: current generic prices



Sofosbuvir: potential generic prices by end 2015



Current costs of sofosbuvir, Per person (12 weeks)



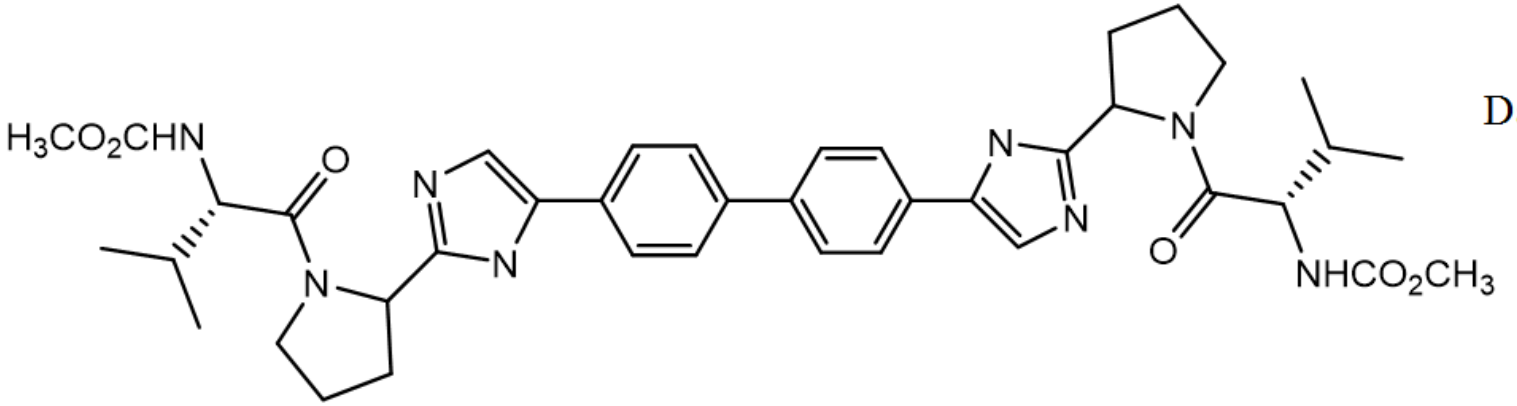
*discount

Minimum cost to produce daclatasvir

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

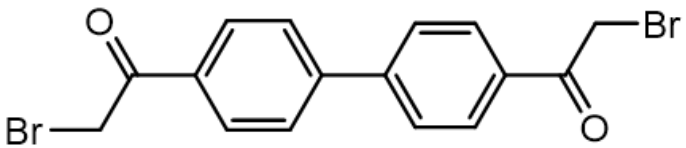
Chemical synthesis: straightforward synthesis given symmetry and availability of cheap starting materials to synthesize the side chains.

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



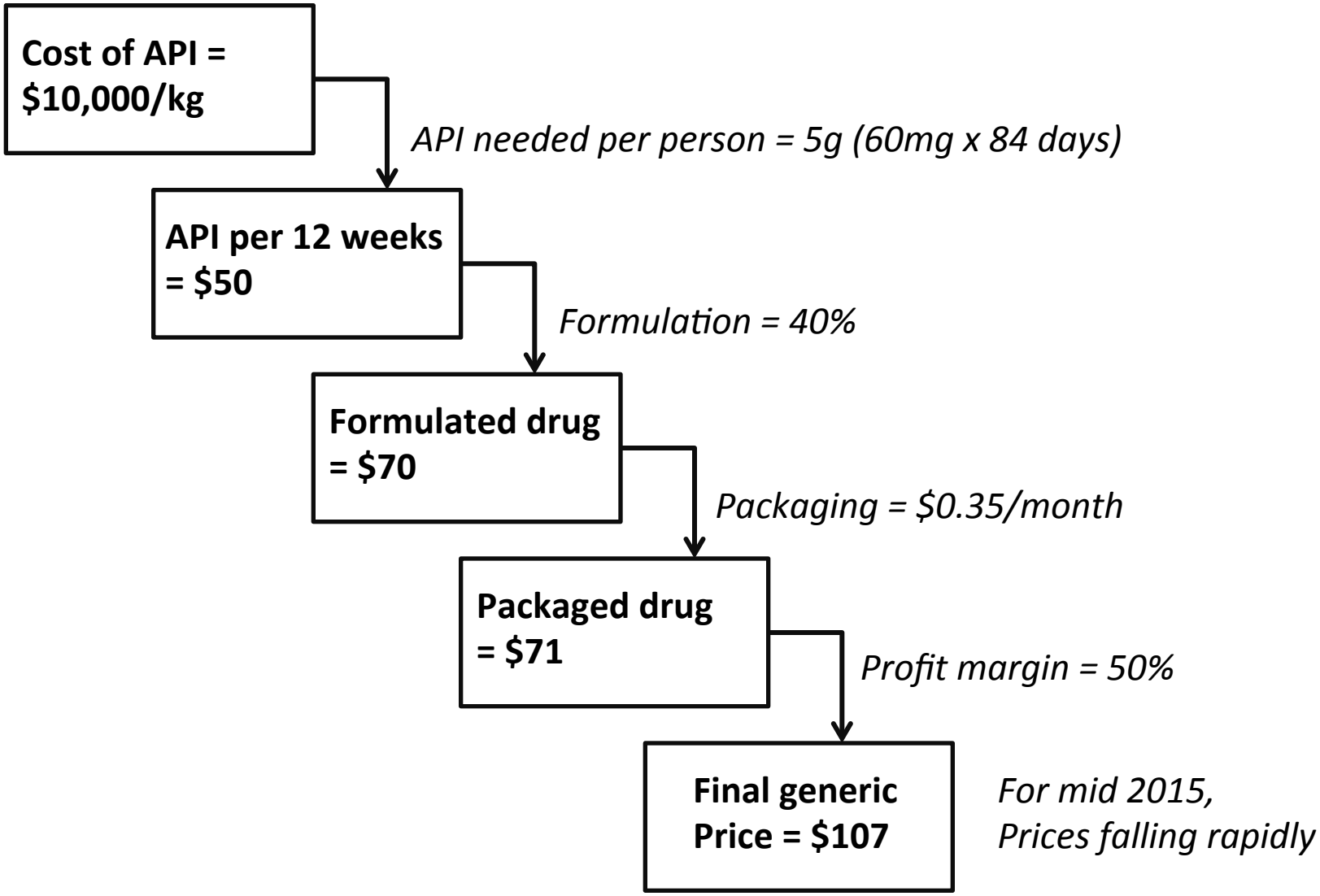
Daclatasvir API

retrosynthesis



Cost-limiting raw material

Daclatasvir: generic prices



5g of diamonds

25 1-carat ($1900 each)

Cost = $48,000

5g of daclatasvir

12 weeks of treatment, 60mg/day

Cost = $53,000 (UK price)

HCV genotypes 1-6 worldwide

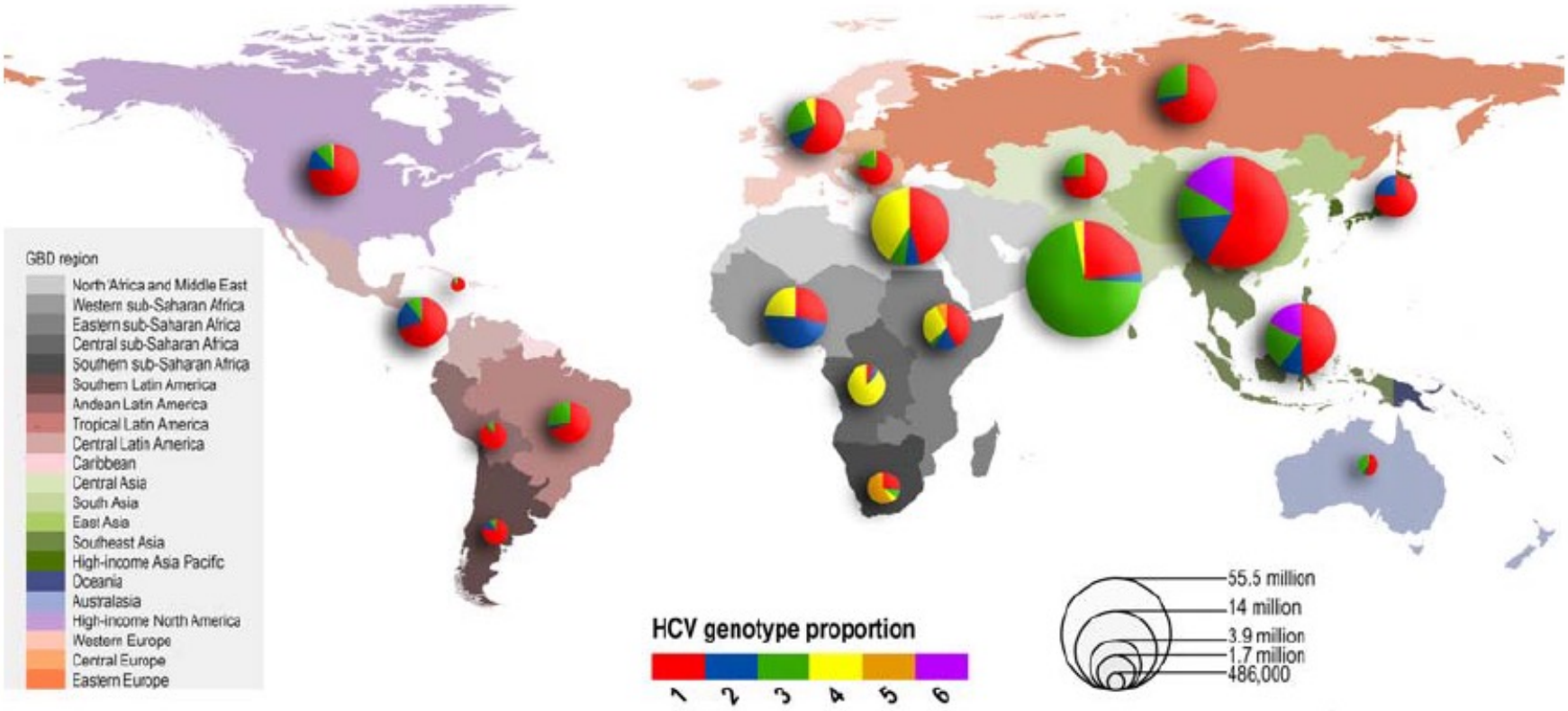
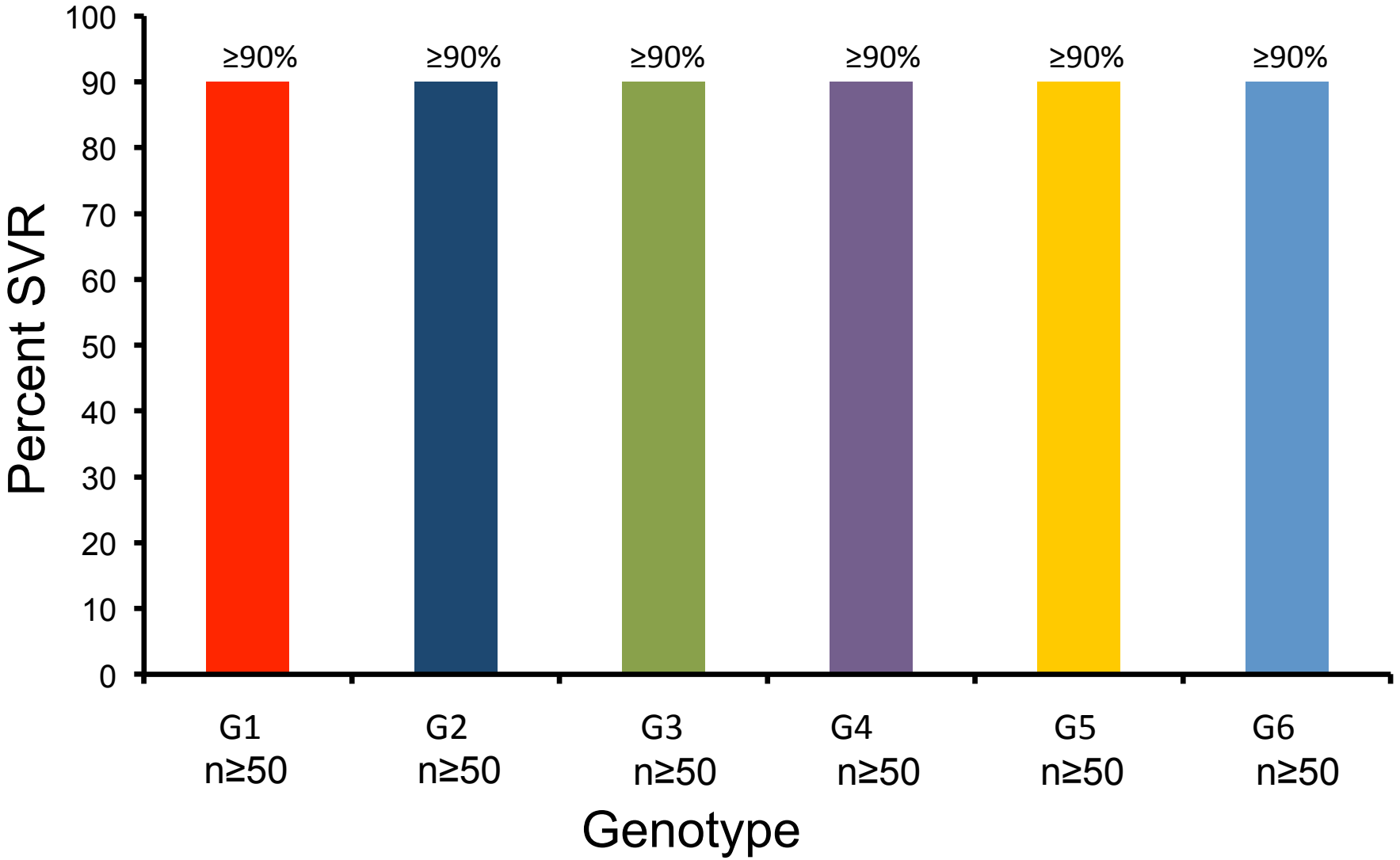
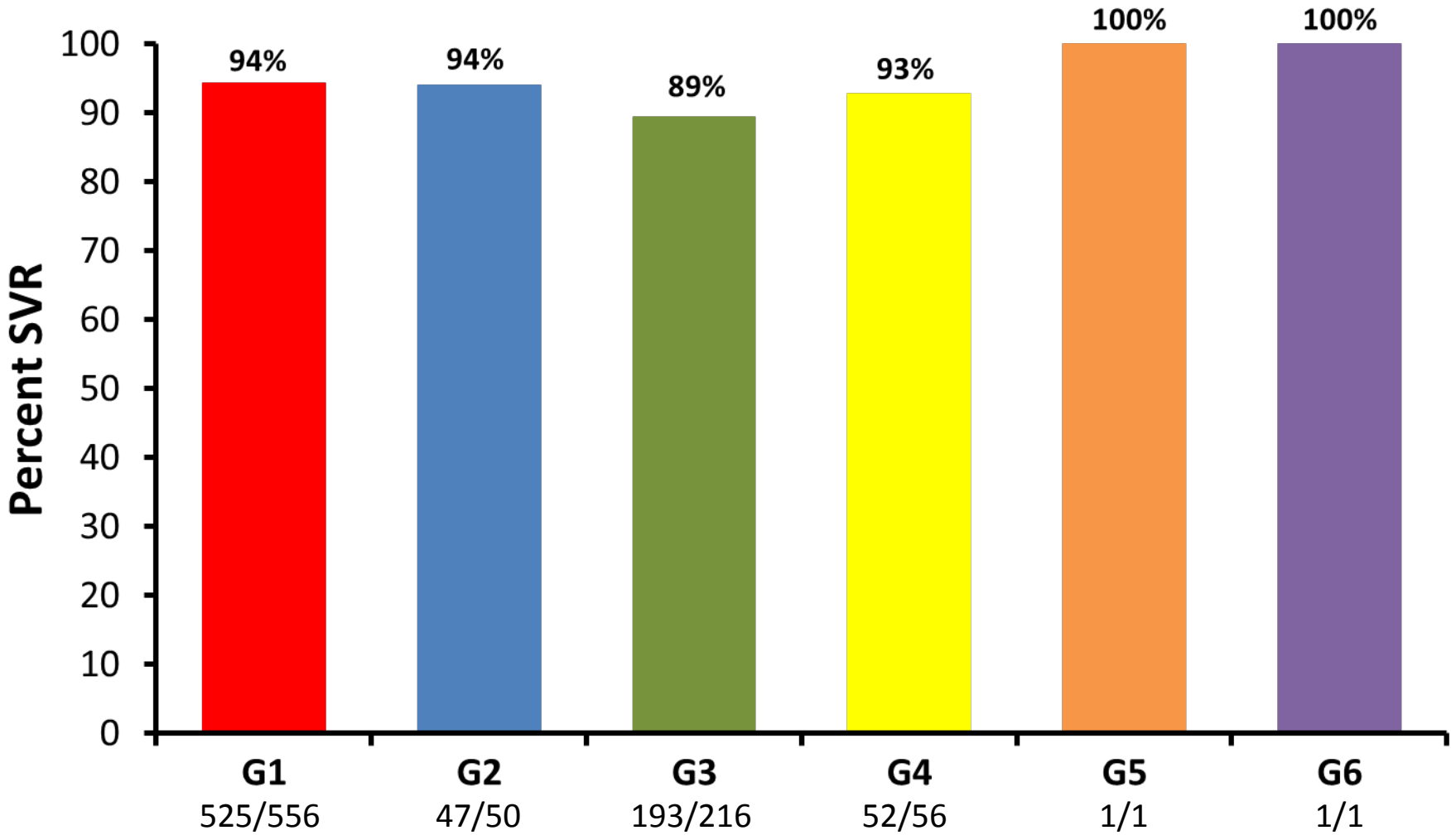


Fig. 1. Relative prevalence of each HCV genotype by GBD region. Size of pie charts is proportional to the number of seroprevalent cas

The ideal DAA treatment: low cost, ≥90% SVR, pan-genotypic, short duration, well tolerated

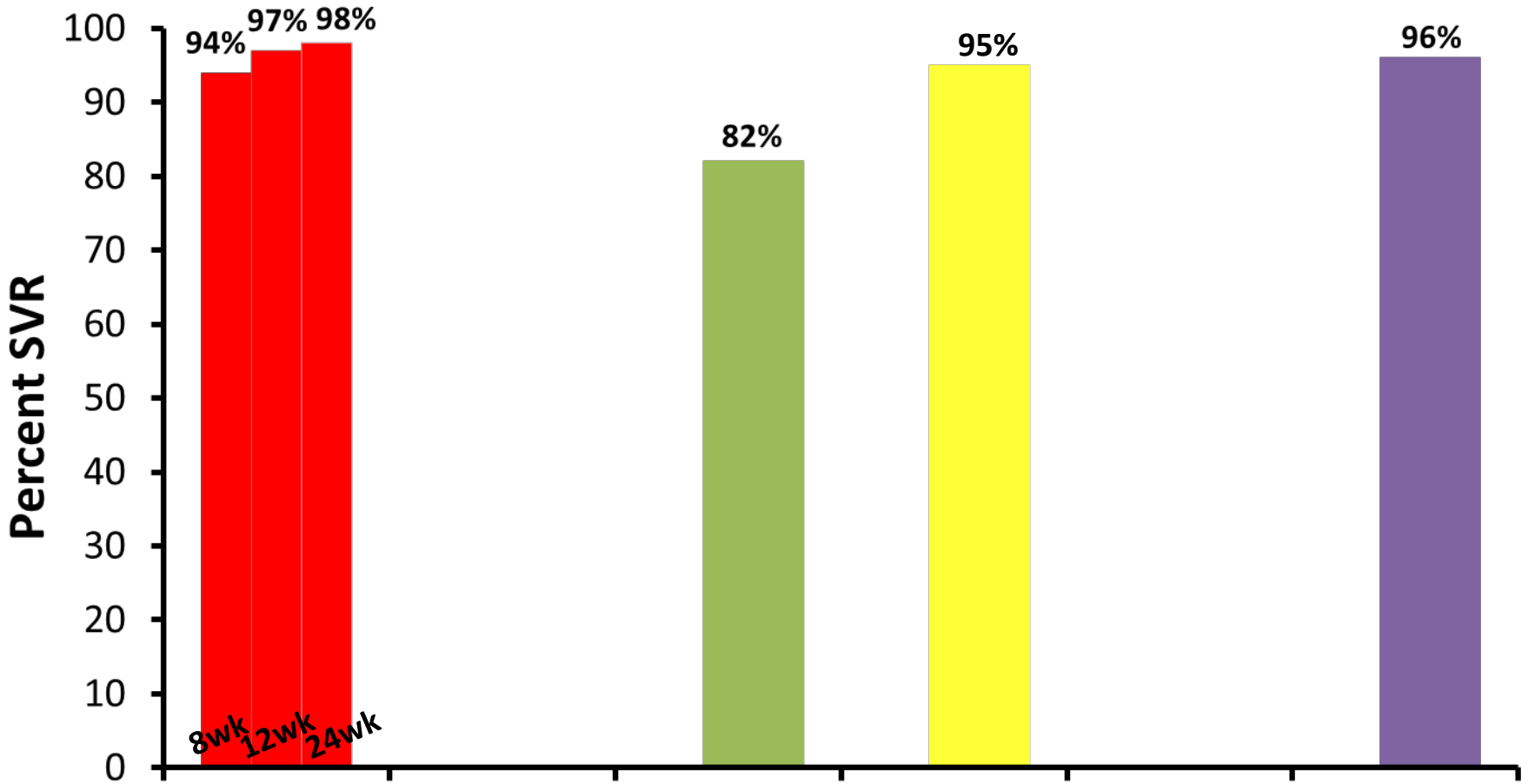


Sofosbuvir + Daclatasvir ± RBV (12 or 24 weeks)



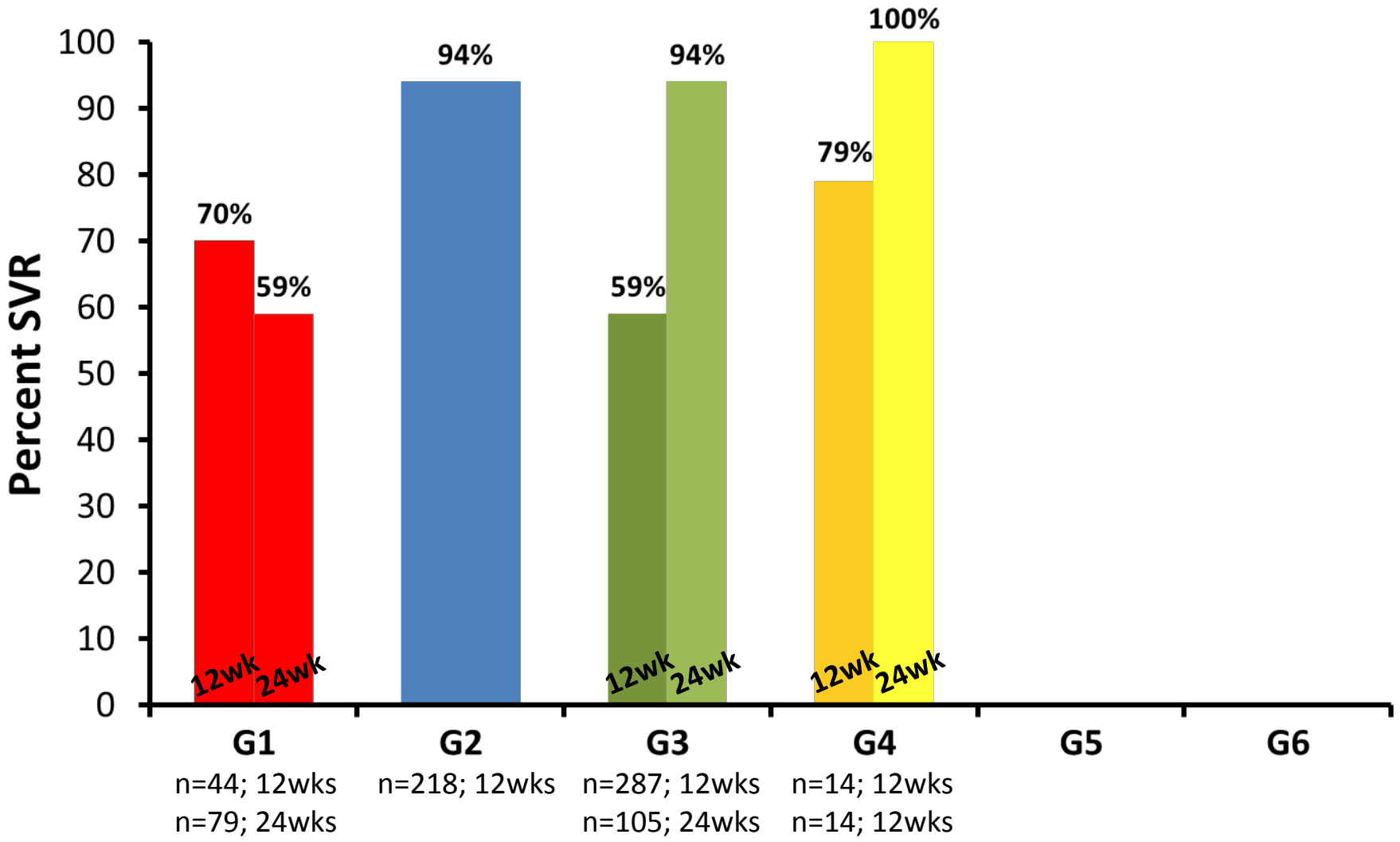
Sources: A1444040 trial; ALLY-1; ALLY-2; ALLY-3; 3 French EAPs

Sofosbuvir + Ledipasvir (± RBV)



Sources: G1: LONESTAR, ION-1, ION-3, ELECTRON, SYNERGY; G3: ELECTRON-2; G4: SYNERGY; G6: Gane et al. (AASLD 2014)

Sofosbuvir + RBV



Sources: G1: SPARE, QUANTUM, VALENCE; G2: POSITRON, VALENCE, FISSION; G3: VALENCE; G4: Ruane et al.

Simplified diagnostic testing for HCV

The favorable safety profiles of new DAA combinations suggest that minimal laboratory monitoring will be necessary to assess safety during treatment.

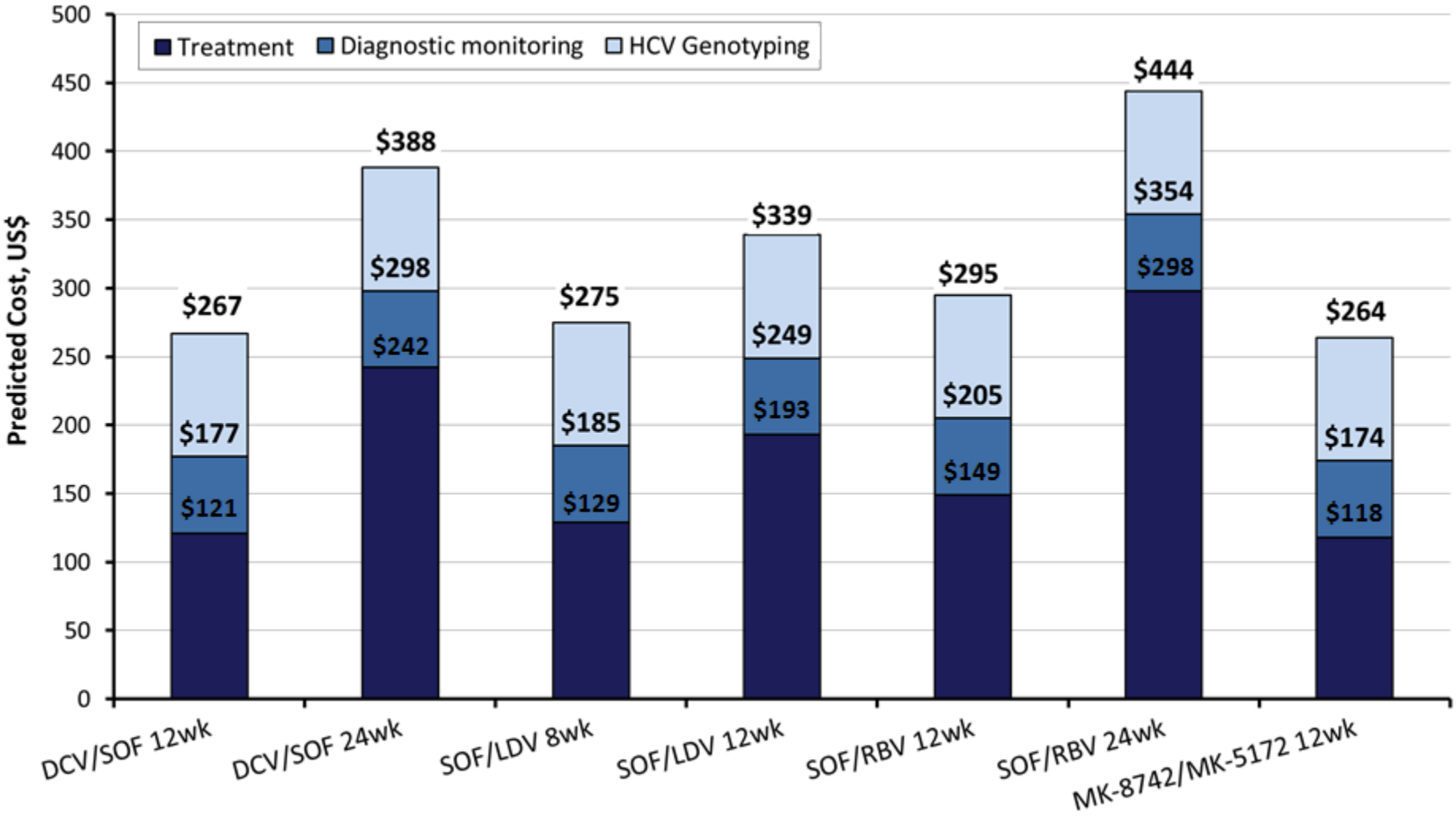
Diagnostics and monitoring could be limited to:

- two HCV antigen tests to confirm chronic infection before treatment and clearance after treatment (detection limit HCV RNA >2000 IU/mL: US$34 for two tests

- two full blood counts + clinical chemistry tests (ALT / creatinine): US$22

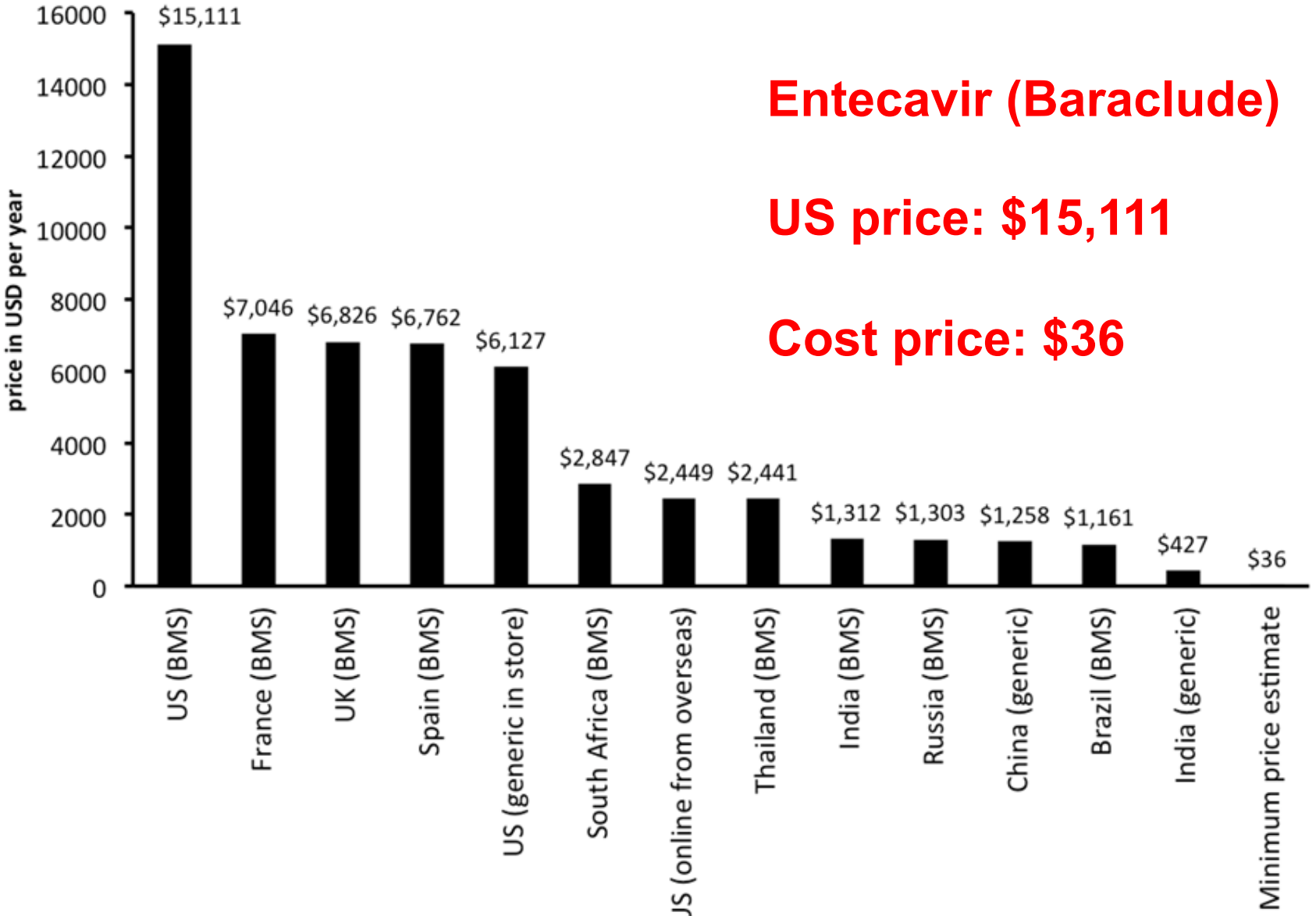
- genotyping if necessary: US$90 (not needed if treatment is pan-genotypic)

Potential minimum costs for treatment and diagnostics, per person – longer-term




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

Entecavir for Hepatitis B
cost per person/year by country



Conclusions

The production price of sofosbuvir is falling rapidly. So far, 3500 kg of sofosbuvir has been exported from India, enough to treat 100,000 people. Even at these small volumes, price/kg is falling to $4000.

This suggests that sofosbubir could be manufactured for $211 per person by end 2015. Daclatasvir is already cheaper than sofosbuvir to manufacture – $107 per person (60mg dose)

Hepatitis B can be also treated for very low costs

These low costs could make universal access to HBV and HCV treatment in lower resource settings a realistic goal.

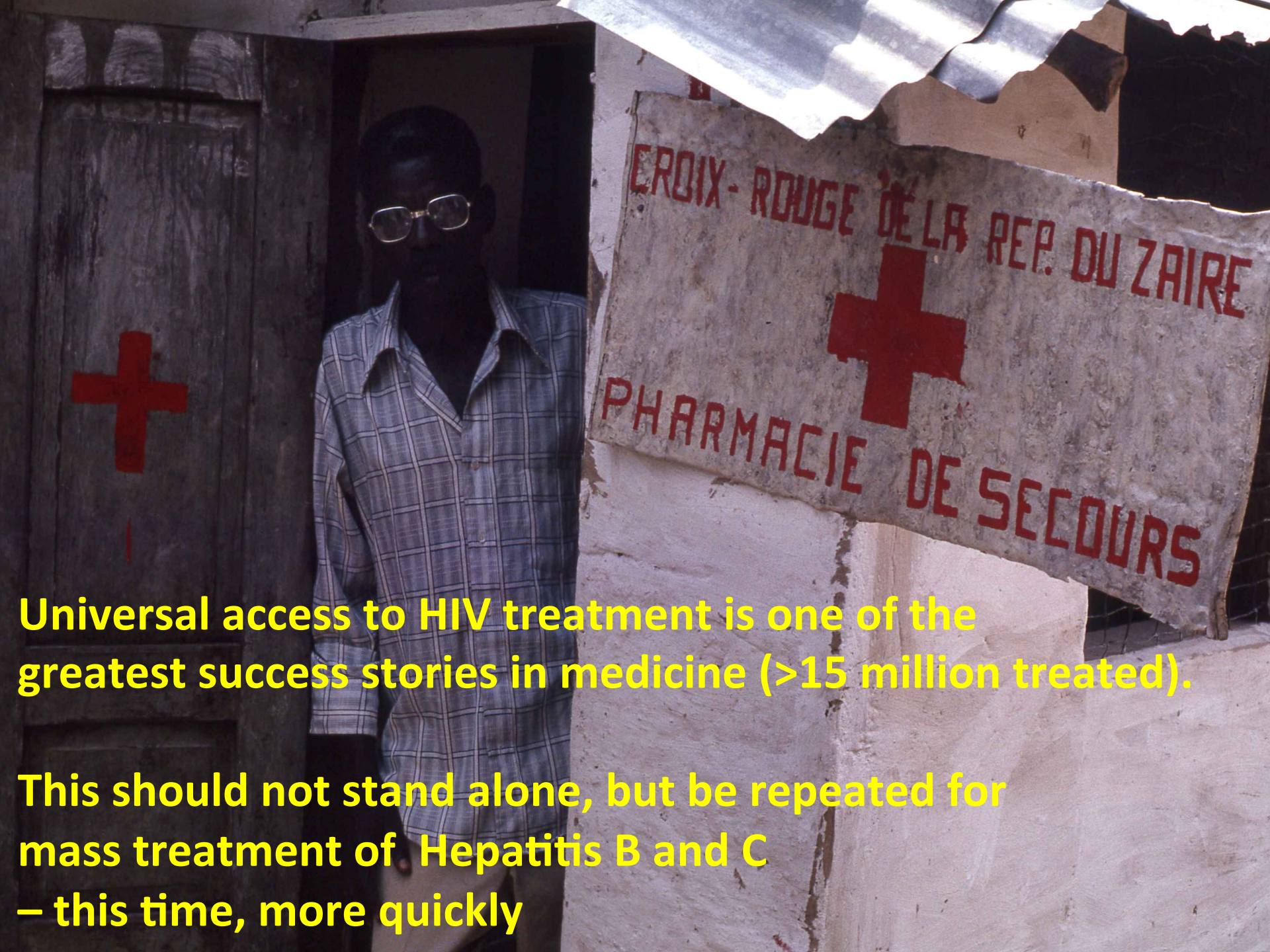
What needs to happen?

1. New funding for HCV treatment to be established at either national or international level, to allow large drug orders to be made, and these economies of scale to be achieved.

2. Clear and transparent treatment access policies with voluntary licensing, from all companies making DAAs (BMS, Merck, AbbVie)

3. Feasibility studies of DAA combinations in LMICs to prove this can be done cheaply

4. Low cost point of care tests to monitor viral load or antigen



Universal access to HIV treatment is one of the greatest success stories in medicine (>15 million treated).

This should not stand alone, but be repeated for mass treatment of Hepatitis B and C – this time, more quickly