Minimum costs to treat viral hepatitis

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

Global Burden of Disease database.

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

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Percent SVR</th>
<th>Subjects/Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>94%</td>
<td>525/556</td>
</tr>
<tr>
<td>G2</td>
<td>94%</td>
<td>47/50</td>
</tr>
<tr>
<td>G3</td>
<td>89%</td>
<td>193/216</td>
</tr>
<tr>
<td>G4</td>
<td>93%</td>
<td>52/56</td>
</tr>
<tr>
<td>G5</td>
<td>100%</td>
<td>1/1</td>
</tr>
<tr>
<td>G6</td>
<td>100%</td>
<td>1/1</td>
</tr>
</tbody>
</table>

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

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

Hill et al.  European AIDS Conference, Barcelona, Spain, October 2015
Current Costs of production - sofosbuvir

Cost of API = $3,493/kg

API needed per person = 34g (400mg x 84 days)

API per 12 weeks = $117

Formulation = 40%

Formulated drug = $164

Packaging = $0.35/month

Packaged drug = $165

Profit margin = 50%

Final generic price = $248

For end 2015, Prices falling rapidly

Hill et al. European AIDS Conference, Barcelona, Spain, October 2015
Minimum cost to produce daclatasvir

**Chemical Formula:** $\text{C}_{40}\text{H}_{50}\text{N}_8\text{O}_6$. 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.

Hill et al. European AIDS Conference, Barcelona, Spain, October 2015
Daclatasvir API exported from India in 2015, weighted by size of shipment

Hill et al. European AIDS Conference, Barcelona, Spain, October 2015
Current Costs of production - daclatasvir

Cost of API = $1,974/kg

API needed per person = 5g (60mg x 84 days)

API per 12 weeks = $9.95

Formulation = 40%

Formulated drug = $14

Packaging = $0.35/month

Packaged drug = $15

Profit margin = 50%

Final generic price = $22

For end2015, Prices falling rapidly
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.
Sofosbuvir (Sovaldi)
US price: $84,000
Cost price: $248
Total sales: >$22 billion
R&D costs: $12 billion
Lowest prices of daclatasvir by country (US dollars per 12 week course)

Daclatasvir (Daklinza)
US price: $63,000
Cost price: $23
Total sales: >$1 billion

Hill et al.  European AIDS Conference, Barcelona, Spain, October 2015
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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>USA</th>
<th>UK</th>
<th>India</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir / Sovaldi</td>
<td>Gilead</td>
<td>$82,446</td>
<td>$53,120</td>
<td>$567</td>
</tr>
<tr>
<td>Pegfiligastra (Neulasta)</td>
<td>Amgen</td>
<td>$61,693</td>
<td>$18,065</td>
<td>$2373</td>
</tr>
<tr>
<td>Etanercept (Enbril)</td>
<td>Immunex</td>
<td>$32,457</td>
<td>$14,115</td>
<td>$12,378</td>
</tr>
<tr>
<td>Glatiramer (Copaxone)</td>
<td>Sandoz</td>
<td>$29,971</td>
<td>$10,176</td>
<td>$6862 (BR)</td>
</tr>
<tr>
<td>Aripiprezole (Ablify)</td>
<td>Otsuka</td>
<td>$4509</td>
<td>$1901</td>
<td>$39</td>
</tr>
<tr>
<td>Insulin (Lantus)</td>
<td>Sanofi</td>
<td>$4605</td>
<td>$805</td>
<td>$473</td>
</tr>
<tr>
<td>Insulin aspart (Novorapid)</td>
<td>Novo Nordisk</td>
<td>$4143</td>
<td>$549</td>
<td>$433</td>
</tr>
</tbody>
</table>
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<th>India</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitaglipin (Januvia)</td>
<td>Merck</td>
<td>$3949</td>
<td>$658</td>
<td>$239</td>
</tr>
<tr>
<td>Pregabalin (Lyrica)</td>
<td>Sandoz</td>
<td>$3767</td>
<td>$1275</td>
<td>$27</td>
</tr>
<tr>
<td>Tiotropium (Spiriva)</td>
<td>Boeringher Ing</td>
<td>$3712</td>
<td>$694</td>
<td>$17</td>
</tr>
<tr>
<td>Fluticazone (Seratide)</td>
<td>GSK</td>
<td>$3701</td>
<td>$647</td>
<td>$178</td>
</tr>
<tr>
<td>Budesonide (Symbicort)</td>
<td>AstraZeneca</td>
<td>$3425</td>
<td>$554</td>
<td>$39</td>
</tr>
<tr>
<td>Rosuvastatin (Crestor)</td>
<td>IPR</td>
<td>$2577</td>
<td>$357</td>
<td>$25</td>
</tr>
</tbody>
</table>
## Costs of monoclonal antibodies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>USA</th>
<th>UK</th>
<th>Brazil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>Genetech</td>
<td>$76,826</td>
<td>$41,057</td>
<td>$39,898</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>Roche</td>
<td>$51,426</td>
<td>$19,301</td>
<td>$10,780</td>
</tr>
<tr>
<td>Adalimumab (Humira)</td>
<td>AbbVie</td>
<td>$36,447</td>
<td>$13,902</td>
<td>$5,396</td>
</tr>
<tr>
<td>Rituximab (MabThera)</td>
<td>Genentech</td>
<td>$23,612</td>
<td>$10,739</td>
<td>$3951</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
<td>Centocor</td>
<td>$8693</td>
<td>$7455</td>
<td>$2,792</td>
</tr>
</tbody>
</table>
Imatinib – for treatment of Leukaemia (CML and ALL)

Annual prices of Imatinib (400mg) in selected countries

- USA (Novartis): $106,322
- South Africa (Novartis): $35,216
- Spain (Novartis): $34,482
- UK (Novartis): $31,867
- France (Novartis): $28,675
- Thailand (Novartis): $20,877
- Russia (Novartis): $8,370
- Brazil (Generic): $8,192
- India (Generic): $790
- Minimum price estimate: $159

Imatinib (Gleevec)
Patent expired (USA)
US price: $106,322/year
Target generic price: $159

Presented at 18th ECCO - 40th ESMO European Cancer Congress,
27th September 2015, Vienna, Austria [abstract number: 1203]
Dasatinib – for treatment of leukaemia

Annual prices of Dasatinib (100mg) in selected countries

- USA GoodRx (BMS): $135,679
- USA NADAC (BMS): $56,970
- Latvia (BMS): $35,048
- Spain (BMS): $35,039
- France (BMS): $33,739
- UK (BMS): $15,423
- Brazil (BMS): $334

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

Presented at 18th ECCO - 40th ESMO European Cancer Congress, 27th 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

% patients after 5 years

General

Cirrhotic

Co-infected

SVR

No SVR
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

% patients after 5 years

<table>
<thead>
<tr>
<th></th>
<th>SVR</th>
<th>No SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>2.9%</td>
<td>9.3%</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>5.3%</td>
<td>13.9%</td>
</tr>
<tr>
<td>Co-infected</td>
<td>0.9%</td>
<td>10.0%</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Group</th>
<th>SVR</th>
<th>No SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>0%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>0.2%</td>
<td>7.3%</td>
</tr>
<tr>
<td>Co-infected</td>
<td>0.6%</td>
<td>2.7%</td>
</tr>
</tbody>
</table>
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

% HCV reinfections after 5 years:
- **Low risk**: 0.9%
- **IVDU / prisoner**: 8.2%
- **HIV co-infected**: 23.6%
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