Hepatitis C:
Short duration DAA therapy, DAA resistance

Graham Cooke
Imperial College, London

14th June, 2016
<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graham Cooke</td>
<td>Consultancy for Gilead, MSD, BI, BMS, Janssen, WHO</td>
</tr>
<tr>
<td></td>
<td>Investigator on studies sponsored by Gilead, Janssen, BMS</td>
</tr>
<tr>
<td>Date</td>
<td>June 2016</td>
</tr>
</tbody>
</table>
Viral Hepatitis 7th leading cause of death

(Mortality rate (per 100,000 py)

- <10
- 10 - 14.9
- 15 - 22.49
- 22.5 - 33.49
- 33.5 +

Proportion attributable to each virus

The area of each pie is proportional to that region's hepatitis-attributable mortality rate. The size of each wedge represents the proportion of that mortality attributable to a given virus.

- hepatitis_a_pr
- hepatitis_b_pr
- hepatitis_c_pr
- hepatitis_e_pr

(Stanaway et al Lancet in press)
Bucking the trend of infectious diseases

Stanaway et al (2015)
Hepatitis has overtaken other major infectious diseases

(GBD 2015 in preparation)
Co-infection in the World

- HCV
- HIV

- 150m
- 36m
- 9%

~3m HCV/HIV co-infected

Platt et al 2016 LID
So what does it tell us about viral hepatitis?

<table>
<thead>
<tr>
<th></th>
<th>Vaccine</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hepatitis E</td>
<td>Yes</td>
<td>(Yes)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
• Treatment is particularly important as a tool to control HCV
It’s about cure = SVR

HIV
- Host cell
- Proviral DNA
- Long-term suppression of viral replication\(^2,3\)

HBV
- Host DNA
- Nucleus
- cccDNA
- Long-term suppression of viral replication

HCV
- Viral RNA
- Viral Eradication = Cure

Genotypes important

cccDNA = covalently closed circular DNA

Why do we want to achieve SVR? All-cause mortality

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

Simmons et al CID 2015
Precision HCV Medicine before “The Storm”

We already (variably) use precision/stratified medicine
Theragnostics and stratification

Starting point-therapy

Therapy responders

Therapy non-responders

Biomarker

Mechanism

If get a biomarker:
• Right existing therapy to the right patients

If get mechanism:
• New therapies for existing non-responders e.g. IFN-lambda

• Attractive to industry
Anticipating the storm:
MRC funding stratified medicine consortia 2013

- Genuinely national consortia that could be outward facing to pharma
- Diseases with strong pipeline of high cost medication
- Required non-cancerous diseases with biological evidence for stratification
How did we achieve SVR back in June 2015 (UK)

<table>
<thead>
<tr>
<th>Pegylated interferon</th>
<th>Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once weekly subcutaneous</td>
<td>Oral</td>
</tr>
<tr>
<td>Immune activation</td>
<td>Antiviral</td>
</tr>
</tbody>
</table>

G1 only
Boceprevir
Telaprevir

G1/4
Simeprevir
Back in 2015: Virus? Q80K and simeprevir

Q80K present in 34% of GT1a patients. No benefit of simeprevir if Q80K positive

Back in 2015: Host genetics? IFNλ3 (IL28) and IFNλ4

Prokunina-Olsson NG (2013)
Hepatitis C: stratification in interferon era

- **Demographic**
  - Age
  - Male gender
  - Ethnicity
- **Clinical**
  - Fibrosis
  - BMI
  - HIV
- **Host genetic**
  - IL28B/IFNL4
- **Viral**
  - Viral resistance mutations
  - Genotype
- **Response guided approaches**
HCV genotypes still matter for now

Messina et al Hepatology (2015)
HCV Genotypes in the UK

General UK population

- G3
- G1

HIV positive population

- G1
- G4

Source: PHE, HCV UK
How relevant is this with new treatments?
HCV lifecycle provides multiple targets for new drugs

Hepatitis C pipeline has been very busy: 2013

NS5A inhibitors

Polymerase inhibitors

Protease inhibitors

DAA combinations

Drug development end 2014

Phase I

Phase II

Phase III

Phase IV

DAA combinations

NS5A inhibitors

Protease inhibitors

Polymerase inhibitors
Field is consolidating

**Phase I**
- Alisporovir (Novartis)
- BIT225 (Biotron)
- IDX 719
- ITX-5061

**Phase II**
- ACH-3102 (Achillon)
- ACH-2684 (Achillon)
- ACH-2686 (Achillon)
- Daclatasvir (BMS)
- GS9857 (Gilead)
- GS9451 (Gilead)
- PPI-461 (Presidio)
- Simeprevir (Janssen)
- Sotuvir (Janssen)
- VX-135 (Vertex)
- VX-222 (Vertex)
- VX-225 (Vertex)

**Phase III**
- Alisporovir (Novartis)
- IDX 719
- ITX-5061
- ACH-3102 (Achillon)
- ACH-2684 (Achillon)
- ACH-2686 (Achillon)
- Daclatasvir (BMS)
- GS9857 (Gilead)
- GS9451 (Gilead)
- PPI-461 (Presidio)
- Simeprevir (Janssen)
- Sotuvir (Janssen)
- VX-135 (Vertex)
- VX-222 (Vertex)

**Phase IV**
- ABT-493/530 (Abbvie)
- BMS-790052/TMC435 (BMS/Tibotec)
- IDX21437 (Merck)
- IDX21459 (Merck)
- VX-222 (Vertex)
- VX-225 (Vertex)

**DAA combinations**
- ACH-2686 (Achillon)
- ACH-3102 (Achillon)
- Daclatasvir/asunaprevir (BMS)
- Daclatasvir/PPI-6618 (Gilead/Presidio)
- GS9857 (Gilead)
- IDX21437/MK drugs (Merck)
- IDX21459 (Merck)
- PPI-461 (Presidio)
- Simeprevir (Janssen)
- Sotuvir (Janssen)
- VX-135 (Vertex)
- VX-222 (Vertex)

**NS5A inhibitors**
- Alisporovir (Novartis)
- IDX 719
- ITX-5061

**Protease inhibitors**
- ACH-3102 (Achillon)
- ACH-2684 (Achillon)
- ACH-2686 (Achillon)
- Daclatasvir (BMS)
- GS9857 (Gilead)
- GS9451 (Gilead)
- PPI-461 (Presidio)
- Simeprevir (Janssen)
- Sotuvir (Janssen)
- VX-135 (Vertex)
- VX-222 (Vertex)

**Polymerase inhibitors**
- Alisporovir (Novartis)
- IDX 719
- ITX-5061
- ACH-3102 (Achillon)
- ACH-2684 (Achillon)
- ACH-2686 (Achillon)
- Daclatasvir (BMS)
- GS9857 (Gilead)
- GS9451 (Gilead)
- PPI-461 (Presidio)
- Simeprevir (Janssen)
- Sotuvir (Janssen)
- VX-135 (Vertex)
- VX-222 (Vertex)
## Selected DAA Combinations in Late Development/ Approval

<table>
<thead>
<tr>
<th>Nucleotide/nucleoside</th>
<th>Non-nucleoside</th>
<th>Protease Inh</th>
<th>NS5a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td></td>
<td>(GS-9857)</td>
<td>Ledipasvir</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td></td>
<td></td>
<td>Velpatasvir</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Dasabuvir</td>
<td>Paritaprevir/R ABT-493</td>
<td>Ombitasvir ABT-530</td>
</tr>
<tr>
<td>(MK-3682)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(MK-3682)</td>
<td>Grazoprevir</td>
<td></td>
<td>Elbasvir</td>
</tr>
<tr>
<td>(MK-3682)</td>
<td>Grazoprevir</td>
<td></td>
<td>MK8408</td>
</tr>
</tbody>
</table>
HCV Genotype 1 Treatment-Naïve Patients – improving SVRs

*Year of data presentation at EASL 2014 and publication in NEJM

Outcomes in HIV very similar to monoinfection
Baseline RAVs (sic) are relatively common

Frequency at baseline

NS5A > NS3 protease > NS5B

Persistence

NS5A > (NS5B) > NS3 protease

Sarrazin et al (2016)
### RAVs differ in frequency across genotype

<table>
<thead>
<tr>
<th>Variant</th>
<th>Gene</th>
<th>1a</th>
<th>1b</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q30H/R/E/L/T</td>
<td>NS5a</td>
<td>0.3%-1.3%</td>
<td>-</td>
<td>-</td>
<td>90.4-100% (Q30A)</td>
<td>50-100% (Q30R)</td>
</tr>
<tr>
<td>L31M</td>
<td>NS5a</td>
<td>0.9-1.8%</td>
<td>2.1-6.3%</td>
<td>74-85%</td>
<td>1%</td>
<td>92.5-100%</td>
</tr>
<tr>
<td>Y93H</td>
<td>NS5a</td>
<td>&lt;1.5%</td>
<td>3.8-14.1%</td>
<td>-</td>
<td>1.3-8.3%</td>
<td>5-13%</td>
</tr>
<tr>
<td>Q80K</td>
<td>NS3</td>
<td>4.8-75%</td>
<td>0.5-1.2%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S282T</td>
<td>NS5B</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
But have relatively limited impact on SVR12

GT 1

96.9% SVR12
n/n=1737/1793

83.9% no NS5A RAV at BL
n=1793

16.1% NS5A RAV
n=344

92.7% SVR12
n/n=319/344

*1% cutoff. BL, baseline.

Sarrazin et al (2014)
Genomics giving us greater understanding of host and virus

Pedergnana et al EASL 2016
Role for precision medicine if very good outcomes?

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>LDV–SOF, 12 Wk</th>
<th>LDV–SOF+RBV, 12 Wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonblack</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon eligibility status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eligible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ineligible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;800,000 IU/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥800,000 IU/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body-mass index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1.5× ULN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1.5× ULN</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>IL28B</em> genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-CC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Afdhal NEJM 2014
Why not give everyone 12 weeks of next generation therapy?
Two big challenges

- Money
- Nature of the therapy (adherence)
Recent case

- 45 year old male ex-IDU
- Chronic HCV (mild disease)
- Pre-existing paranoid ideation
- Baseline HCV VL 6000000 IU/l, genotype 1a
- Started OMB/PAR/DAS/RIT/RBV
- Stopped treatment early at 3/52
- Achieved SVR12

Could we have known before treatment started that 3/52 would be enough?
Money:
Not just a UK problem
The cost of sofosbuvir for Hepatitis C per person, 12 weeks treatment

- USA: $84,000
- Germany: $67,000
- UK: $57,000
- Egypt: $1,000
- Minimum: $68-$136

Hill & Cooke (Science 2014)
215,000 \times £25,000 = £5.4 billion
= £216m \times 25 \text{ years}
Cost and convenience

Drug spending, 2016 forecast
% change on a year earlier

Hepatitis C
Cystic fibrosis*
Cancer
Asthma
Depression
High cholesterol

Source: Express Scripts  *And other respiratory conditions

Economist 2014
I. Gardini, on behalf of ELPA. January 2016

**Restrictions for access to HCV innovative drugs 2° generation**

**Europe, Balkans, Switzerland**

<table>
<thead>
<tr>
<th>Country</th>
<th>Restrictions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>Drug users and prisoners are still excluded in real life. Some complexity with insurances</td>
</tr>
<tr>
<td>Portugal</td>
<td>Some drugs need special authorization</td>
</tr>
<tr>
<td>Poland</td>
<td>Some limitations for F0 patients</td>
</tr>
<tr>
<td>France</td>
<td>All HIV/HCV coinfected + symptomatic cryoglobulimea + Lymphoma can be treated w/o restrictions</td>
</tr>
<tr>
<td>Croatia</td>
<td>Naive and G3 patients it is still P/R first line. F3 and F4 patients has priority</td>
</tr>
<tr>
<td>Greece</td>
<td>F3 patients can be treated only if failed in the past</td>
</tr>
<tr>
<td>Hungary</td>
<td>Naive pt treated with PEG+RBV, tx and pt with IFN-contraindication treated with IFN-free independently</td>
</tr>
<tr>
<td>UK</td>
<td>From Beginning of March all G1s will get Harvoni or AbbVie 3D. Other GT waiting for Velpatasvir</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>Some drugs approved, Defining the access criteria</td>
</tr>
<tr>
<td>Spain</td>
<td>Extrahepatic manifestations and/ or high risk of infectivity with F0-F1</td>
</tr>
<tr>
<td>Italy</td>
<td>Tx and pt with severe extra hepatic diseases can be treated independently fibrosis stage. F0-F2 can be treated with INF, RIBA and SIMPEREVIR</td>
</tr>
<tr>
<td>Finland</td>
<td>All naive pt. GT1,2,3 start with INF+RIBA. If negative w/e 4 continue.F3-F4 Stop</td>
</tr>
</tbody>
</table>

*Informations given by ELPA members, and taken from presentations and internet research*
## England: Run rates

<table>
<thead>
<tr>
<th>ODN</th>
<th>Region</th>
<th>Prevalence²</th>
<th>Confirmed</th>
<th>Provisional</th>
<th>Annual Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Q1 2000</td>
<td>Q2 2500</td>
<td>Q3 2650</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Apr May Jun</td>
<td>Jul Aug Sep</td>
<td>Oct Nov Dec</td>
</tr>
<tr>
<td>1.</td>
<td>North East &amp; Cumbria</td>
<td>North</td>
<td>4.4%</td>
<td>29 29 29</td>
<td>37 37 37</td>
</tr>
<tr>
<td>2.</td>
<td>Greater Manchester &amp; Eastern Cheshire</td>
<td>North</td>
<td>7.5%</td>
<td>50 50 50</td>
<td>62 62 62</td>
</tr>
<tr>
<td>3.</td>
<td>Cheshire &amp; Merseyside</td>
<td>North</td>
<td>4.5%</td>
<td>30 30 30</td>
<td>38 38 38</td>
</tr>
<tr>
<td>4.</td>
<td>South Yorkshire</td>
<td>North</td>
<td>4.1%</td>
<td>27 27 27</td>
<td>34 34 34</td>
</tr>
<tr>
<td>5.</td>
<td>Humberside and North Yorkshire</td>
<td>North</td>
<td>4.1%</td>
<td>27 27 27</td>
<td>34 34 34</td>
</tr>
<tr>
<td>6.</td>
<td>West Yorkshire</td>
<td>North</td>
<td>7.0%</td>
<td>47 47 47</td>
<td>59 59 59</td>
</tr>
<tr>
<td>7.</td>
<td>Lancashire and South Cumbria</td>
<td>North</td>
<td>4.3%</td>
<td>29 29 29</td>
<td>36 36 36</td>
</tr>
<tr>
<td>8.</td>
<td>Leicester</td>
<td>North</td>
<td>2.7%</td>
<td>18 18 18</td>
<td>22 22 22</td>
</tr>
<tr>
<td>9.</td>
<td>Birmingham</td>
<td>Midlands</td>
<td>8.7%</td>
<td>58 58 58</td>
<td>73 73 73</td>
</tr>
<tr>
<td>10.</td>
<td>Nottingham</td>
<td>Midlands</td>
<td>3.8%</td>
<td>26 26 26</td>
<td>32 32 32</td>
</tr>
<tr>
<td>11.</td>
<td>Eastern Hepatitis Network</td>
<td>Midlands</td>
<td>6.0%</td>
<td>40 40 40</td>
<td>50 50 50</td>
</tr>
<tr>
<td>12.</td>
<td>West London</td>
<td>London</td>
<td>4.8%</td>
<td>32 32 32</td>
<td>40 40 40</td>
</tr>
<tr>
<td>13.</td>
<td>North Central London</td>
<td>London</td>
<td>7.5%</td>
<td>50 50 50</td>
<td>63 63 63</td>
</tr>
<tr>
<td>14.</td>
<td>Barts</td>
<td>London</td>
<td>5.0%</td>
<td>33 33 33</td>
<td>42 42 42</td>
</tr>
<tr>
<td>15.</td>
<td>South Thames Hepatitis Network (STHepNet) Kings &amp; St George’s</td>
<td>London</td>
<td>9.5%</td>
<td>63 63 63</td>
<td>79 79 79</td>
</tr>
<tr>
<td>16.</td>
<td>Surrey Hepatitis Services</td>
<td>South</td>
<td>1.8%</td>
<td>12 12 12</td>
<td>15 15 15</td>
</tr>
<tr>
<td>17.</td>
<td>Sussex Hepatology Network</td>
<td>South</td>
<td>1.8%</td>
<td>12 12 12</td>
<td>15 15 15</td>
</tr>
<tr>
<td>18.</td>
<td>Oxford University Hospitals NHS Trust - Thames Valley</td>
<td>South</td>
<td>3.6%</td>
<td>24 24 24</td>
<td>30 30 30</td>
</tr>
<tr>
<td>19.</td>
<td>Wessex Hep C ODN</td>
<td>South</td>
<td>3.2%</td>
<td>22 22 22</td>
<td>27 27 27</td>
</tr>
<tr>
<td>20.</td>
<td>Bristol and Severn Hep C ODN</td>
<td>South</td>
<td>1.7%</td>
<td>11 11 11</td>
<td>14 14 14</td>
</tr>
<tr>
<td>21.</td>
<td>South West Peninsula Hepatitis C ODN</td>
<td>South</td>
<td>2.3%</td>
<td>15 15 15</td>
<td>19 19 19</td>
</tr>
<tr>
<td>22.</td>
<td>Kent Network via Kings</td>
<td>South</td>
<td>1.8%</td>
<td>12 12 12</td>
<td>15 15 15</td>
</tr>
</tbody>
</table>

Goal 666 666 666 834 834 834 885 885 885 952 952 952 10,011
Overcoming the cost barriers to improve access

- More competition from manufacturers
- Value based pricing and other funding structures (“Australia model”), France, Ireland
- NGO activity (activism)
- Access to generic treatments from outside EU (gathering momentum)
- Making smarter use of the treatments we have
We will be overtreating most patients despite the costs
A challenge common to many infectious diseases

This is true in

<table>
<thead>
<tr>
<th>Disease</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB</td>
<td>6-24/12</td>
</tr>
<tr>
<td>Sepsis and bacterial infection</td>
<td>7-21d</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>8-12/52</td>
</tr>
</tbody>
</table>

Our evidence base for predicting who will be cured with shorter duration of therapy is not often good enough to change practice.
Most patients will get too much HCV treatment.
What is the relationship between duration and cure?

![Graph showing the relationship between weeks of treatment and probability of cure. The graph indicates that as the weeks of treatment increase, the probability of cure also increases.]
Selected studies on shortened DAA therapy

**Acute HCV (small studies)**

SLAM-C
Gilead 6/52 study

**Recent HCV**

TARGET 3D

**Chronic HCV / HIV**

STOP HCV-1
SLAM-C : Pilot short course in IDU

Inclusion

Largely non-Caucasian males

HIV negative, acute HCV active IDU

Baseline VL mean 1.2/1.6 million

Intervention

A) 4/52 SOF/LDV

B) 8/52 SOF/SIM

Basu et al APASL 2016
<table>
<thead>
<tr>
<th>Undetectable</th>
<th>Group A SOF/LDV 4/52 N=14</th>
<th>Group B SOF/SIM 8/52 N=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 7</td>
<td>13/14 (92.9%)</td>
<td>13/15 (86.7%)</td>
</tr>
<tr>
<td>EOT</td>
<td>14/14 (100%)</td>
<td>14/15 (93.3%)</td>
</tr>
<tr>
<td>SVR12</td>
<td>14/14 (100%)</td>
<td>13/13 (100%)</td>
</tr>
<tr>
<td>Retention</td>
<td>13/14 (92.9%)</td>
<td>13/15 (86.7%)</td>
</tr>
</tbody>
</table>
Gilead 6/52 pilot in acute HCV/HIV

Inclusion

Male, mostly caucasian

Median baseline VL <1 million

N=26 LDV/SOF FDC

SVR12

Nelson et al BHIVA Thurs
Results: SVR4 and SVR12

*3 patients relapsed, 1 was reinfected (GT 1a at baseline, 4d in post-treatment).

Error bars represent 95% confidence intervals.
Points worth noting

No resistance identified

SVR 77% reduced by LFTU and reinfection

Lower SVR that SLAM-C, possibly reflecting VL

All relapsers have baseline VL >10 million
We can do better: redefining stratification in IFN free era

Baseline stratification; Viral load thresholds for Harvoni
Viral resistance testing for Graz/Elb

On treatment responses; data emerging

Treatment/Retreatment; SYNERGY, C-SWIFT
Hepatitis C genotype 1a/1b
Mild disease (fibroscan). Mono- and co-infection
No drug-drug interactions with concomitant medications
(n=408)

Factorial randomisation

4-6 weeks A3D
Stratified by Screening
HCV VL
± ribavirin

8 weeks A3D
Fixed duration
± ribavirin

SVR12?**

Follow-up: day 3, 7, 14, 28: then every other week until 4 weeks post end of treatment; then 4-weekly until 12 weeks post end of treatment, then 24 weeks 24 post end of treatment.

Primary endpoint: Overall SVR12 (ie cure) at the end of first-line and any re-treatment (stratified randomisation)
SVR12 at the end of first-line (ribavirin comparison)

Secondary endpoints: SVR24; lack of initial virological response; viral load rebound (relapse) after becoming undetectable; serious adverse events; grade 3 or 4 adverse events; adverse events of any grade judged definitely/ probably related to the intervention; treatment-modifying toxicity of any grade; grade 3 or 4 anaemia; emergence of resistance-associated Hepatitis C variants; cost.

**not achieving SVR12= failure to suppress virus during treatment; relapse after suppression either prior to or at week 12 after end of therapy.
- Key difference from the same challenges posed in other infections (e.g. TB, sepsis)

- Merck’s C-SWIFT (ELB/GRAZ/SOF) studied durations down to 4/52

  Retreatment of failures presented in AASLD – 100% SVR

- NIH/Gilead Synergy Study also down to 4/52

  Retreatment success of over 90% despite high rates of NS5a emergence
Emergence of RAVs after short course Rx

Slide courtesy of Eleanor Wilson
Open for recruitment at two sites, others in set-up

All but one of the ODN in England have expressed interest

Supported by MRC, NIHR and NHS England

Wales and Scotland too

Currently navigating recruitment within NHSE restrictions on treatment
Where do we want to get to?
Where do we want to get to?
Where do we want to get to?

We want to be able to offer all patients >90% chance of cure with minimum duration of therapy

Leverage expertise in genetics (viral>host) and immunology to support this in routine practice

Achieve this through further studies

- To evaluate other genotypes
- To validate rules for shortened treatment with goal of >90%

Integrate with developments in informatics

UK system should be better placed than anyone to do this
Thank you

IHME, Seattle
Mohsen Naghavi
Abraham Flaxman
Jeff Stanaway
Theo Vos
GBD Collaborators

WHO
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Stefan Wiktor

Microhaart
Andrew Hill
Bryony Wilkes

MRC Clinical Trials@UCL
Sarah Walker
Sarah Pett

STOP HCV Consortium
Ellie Barnes
Will Irving
John Mclauchlan
Peter Vickerman
Peter Simmonds
Paul Klenerman
Graham Foster

STOPHCV1 Investigators

MSF
Bhargavi Rao
Philipp du Cros
Jen Cohn

Imperial College/ICHT
Borja Mora-Peris
Scott Mullaney
Ken Legg
Nur Johari
Janice Main
Mark Thursz
Ashley Brown
Simon Taylor-Robinson
Shahid Khan
Maud Lemoine

Q &A
Major impact on access in US systems

Barua et al JAMA 2015
Bucking the trend of infectious diseases

Stanaway et al (2015)
Costs

HCV: Sofosbuvir
\( C_{22}H_{29}FN_3O_9P \)
Molecular weight: 529 g/mol
34g per treatment course

HIV: Tenofovir disoproxil fumarate (TDF)
\( C_{23}H_{34}N_5O_{14}P \)
Molecular weight: 636 g/mol
$0.52 per gram

Hill et al CID 2014
<table>
<thead>
<tr>
<th>HCV DAA</th>
<th>Daily dose</th>
<th>Total dose (12wk)</th>
<th>Predicted cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribavirin</td>
<td>1000mg</td>
<td>84g</td>
<td>$21-63*</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>60mg</td>
<td>5g</td>
<td>$10-30</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>400mg</td>
<td>34g</td>
<td>$68-136</td>
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<tr>
<td>Faldaprevir</td>
<td>120mg</td>
<td>10g</td>
<td>$100-210</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>150mg</td>
<td>13g</td>
<td>$130-270</td>
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</tbody>
</table>

*$25-76 for 1200mg daily dose of ribavirin
Factors considered in pricing of HCV drugs

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<tr>
<th>Stakeholders</th>
<th>Wave 1 Regimen</th>
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<tr>
<td></td>
<td>$60,000</td>
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<tr>
<td></td>
<td>$50,000</td>
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<tr>
<td></td>
<td>$70,000</td>
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<tr>
<td>Payers</td>
<td></td>
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<tr>
<td>Likelihood of applying</td>
<td>Unlikely</td>
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<tr>
<td>directly observed therapy</td>
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<tr>
<td>due to high price</td>
<td>Likely</td>
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<td>Physicians</td>
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<td>Likelihood of delay treatment</td>
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<tr>
<td>of GT-1 TN patients due to</td>
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<tr>
<td>pricing</td>
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<tr>
<td>Likelihood of losing some</td>
<td>Very Unlikely</td>
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<tr>
<td>KOL endorsement/support</td>
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<td>as price too high</td>
<td>Likely</td>
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<tr>
<td>Patients and Advocacy groups</td>
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<tr>
<td>Likelihood of AHF, FPC and</td>
<td>Likely</td>
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<tr>
<td>other advocacy groups reacting</td>
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<tr>
<td>negatively to price, and</td>
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<tr>
<td>affecting public opinion</td>
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<tr>
<td>Higher out-of-pocket costs</td>
<td>Very Unlikely</td>
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<tr>
<td>(not offset by patient</td>
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<tr>
<td>support) could drive patient</td>
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<td>choice away from SOF,</td>
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<tr>
<td>especially AbbVie has great</td>
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<td>Likelihood of AHF, FPC and</td>
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<td>promote AbbVie products due</td>
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<td>to the relationship and lower</td>
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<td>Treatment Guidelines</td>
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<td>Likelihood of AASLD develop</td>
<td>Possible</td>
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<td>treatment pathway to</td>
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<td>prioritize (staging) patients</td>
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<td>(per KOLs or/and professional</td>
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<tr>
<td>community request)</td>
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<tr>
<td>Others</td>
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<tr>
<td>Likelihood of a &quot;price</td>
<td>Unlikely</td>
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<tr>
<td>mention or asterisk&quot; in</td>
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<td>professional community</td>
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<td>request)</td>
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<tr>
<td>Likelihood of public outcry</td>
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<td>if SOF revenue exceed $2B</td>
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<td>as government trying to</td>
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<td>Likelihood of a letter from</td>
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<td>congress on SOF price</td>
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<tr>
<td>Likelihood of a congressional</td>
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<tr>
<td>hearing if SOF revenue</td>
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<tr>
<td>exceed $2B</td>
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