Shorter Durations and Pan-genotypic Regimens

*The Final Frontier*

Professor Greg Dore
Disclosures

- Funding and speaker fees from AbbVie, Bristol-Myers Squibb, Gilead Sciences and Merck
Evolution of HCV therapies

Adapted from Dore G, Feld JJ. Clin Infect Dis 2015;60:1829–36
DAA agents: licensed and in development

Simeprevir
Paritaprevir
Grazoprevir
Voxilaprevir
Glecaprevir

Ledipasvir
Daclatasvir
Ombitasvir
Elbasvir
Velpatasvir
Pibrentasvir
Ruzasvir

Sofosbuvir
Dasabuvir
Uprifosbuvir
In pursuit of *Perfectovir*

- Extremely high efficacy (>95%)
- No impact of resistance-associated substitutions
- Pan-genotypic
- Tolerance similar to placebo
- Simplified assessment and monitoring
- Ease of delivery (once daily, oral, short duration)
- Affordable!
In pursuit of *Perfectovir*

- Extremely high efficacy (>95%)
- No impact of resistance-associated substitutions
- Pan-genotypic
- Tolerance similar to placebo
- Simplified assessment and monitoring
- Ease of delivery (once daily, oral, *short duration*)
- Affordable!
Sofosbuvir/Velpatasvir

GT1-6, treatment naïve and IFN exp. (28%), F0-4 (21% F4), 12 wks

## Sofosbuvir/Velpatasvir

### Adverse Events >10%

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>SOF/VEL 12 Week N=1035</th>
<th>Placebo 12 Week N=116</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>296 (29)</td>
<td>33 (28)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>217 (21)</td>
<td>23 (20)</td>
</tr>
<tr>
<td>Nausea</td>
<td>135 (13)</td>
<td>13 (11)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>87 (8)</td>
<td>11 (9)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>121 (12)</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Cough</td>
<td>57 (6)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Irritability</td>
<td>49 (5)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>33 (3)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>33 (2)</td>
<td>4 (3)</td>
</tr>
</tbody>
</table>
In pursuit of *Perfectovir*

- Extremely high efficacy (>95%)
- Incredibly well tolerated (similar to placebo)
- Pan-genotypic
- No significant impact of resistance-associated substitutions
- Simplified assessment and monitoring
- Ease of delivery (once daily, oral, short duration)
- Affordable!
Is the pursuit of shorter duration DAA therapy a major priority for Global HCV Elimination?
<table>
<thead>
<tr>
<th>Potential Pros and Cons of Shorter Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOF/VEL (12 weeks)</strong></td>
</tr>
<tr>
<td><strong>Shorter Duration (4-8 weeks)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
## Potential Pros and Cons of Shorter Duration

<table>
<thead>
<tr>
<th></th>
<th>SOF/VEL (12 weeks)</th>
<th>Shorter Duration (4-8 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covers all major sub-populations</td>
<td>YES</td>
<td>Unlikely</td>
</tr>
</tbody>
</table>
## Potential Pros and Cons of Shorter Duration

<table>
<thead>
<tr>
<th></th>
<th>SOF/VEL (12 weeks)</th>
<th>Shorter Duration (4-8 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covers all major sub-populations</td>
<td>YES</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Simplicity</td>
<td>HIGH</td>
<td>Lower</td>
</tr>
</tbody>
</table>
### Potential Pros and Cons of Shorter Duration

<table>
<thead>
<tr>
<th>Feature</th>
<th>SOF/VEL (12 weeks)</th>
<th>Shorter Duration (4-8 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covers all major sub-populations</td>
<td>YES</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Simplicity</td>
<td>HIGH</td>
<td>Lower</td>
</tr>
<tr>
<td>Toxicity</td>
<td>MINIMAL</td>
<td>May be increased or decreased</td>
</tr>
</tbody>
</table>
## Potential Pros and Cons of Shorter Duration

<table>
<thead>
<tr>
<th></th>
<th>SOF/VEL (12 weeks)</th>
<th>Shorter Duration (4-8 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covers all major sub-populations</td>
<td>YES</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Simplicity</td>
<td>HIGH</td>
<td>Lower</td>
</tr>
<tr>
<td>Toxicity</td>
<td>MINIMAL</td>
<td>May be increased or decreased</td>
</tr>
<tr>
<td>Non-adherence “Forgiveness”</td>
<td>Probably HIGH</td>
<td>May be lower</td>
</tr>
</tbody>
</table>
Sofosbuvir/Velpatasvir/Voxilaprevir

POLARIS 2: GT1-6, DAA naive, F0-4 (18% F4, 0% GT3), 8 weeks

SVR12 %

95% (95% CI 93-97%)          98% (95% CI 96-99%)

476/501                      432/440

SOF/VEL/VOX 8 weeks          SOF/VEL 12 weeks

Sofosbuvir/Velpatasvir/Voxilaprevir

POLARIS 2: GT1-6, DAA naive, F0-4 (18% F4, 0% GT3), 8 weeks

SOF/VEL/VOX 8 weeks

SOF/VEL 12 weeks

SVR12 %

GT1a 155/169 170/172
GT1b 61/63 57/59
GT2 61/63 53/53
GT3 91/92 86/89
GT4 58/63 56/57
Other* 50/51 9/9

* 2 Other GT1, 18 GT5, 39 GT6 (9/9 SOF/VEL)

## Sofosbuvir/Velpatasvir/Voxilaprevir

**POLARIS 2: Adverse Events >10%**

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>SOF/VEL/VOX 8 Week N=501</th>
<th>SOF/VEL 12 Week N=440</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>134 (27)</td>
<td>99 (23)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>106 (21)</td>
<td>90 (20)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>88 (18)</td>
<td>32 (7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>80 (16)</td>
<td>40 (9)</td>
</tr>
<tr>
<td>Any Adverse Event</td>
<td>361 (72)</td>
<td>303 (69)</td>
</tr>
<tr>
<td>Serious Adverse Events</td>
<td>15 (3)</td>
<td>7 (2)</td>
</tr>
</tbody>
</table>
Glecaprevir/Pibrentasvir

GT1-6, treatment naïve, F0-3, 8 and 12 weeks in Phase II/III trials

Kwo P, J Hepatology 2017; Zeuzem S, AASLD 2016; Kowdley K, AASLD 2016; Asselah T, AASLD 2016; Gane E, AASLD 2016; Foster G, ILC 2017
## ENDURANCE 2: Adverse Events

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>GLE/PIB 12 Week N=202</th>
<th>Placebo 12 Week N=100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>24 (12)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23 (11)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Any Adverse Event</td>
<td>131 (65)</td>
<td>58 (58)</td>
</tr>
<tr>
<td>Serious Adverse Events</td>
<td>3 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>ALT (&gt;3xULN)</td>
<td>1 (0.5)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Bilirubin (3-10xULN)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
230,000
Australians live with chronic HCV infection

HCV care cascade in Australia: end 2015

- Pre-cirrhosis, naive
- Pre-cirrhosis, experienced
- Cirrhosis
HCV care cascade in Australia: end 2016

200,000
Australians live with chronic HCV infection

- Pre-cirrhosis, naive
- Pre-cirrhosis, experienced
- Cirrhosis
Where would shorter durations (4-6 weeks) help?

- Prisons, particularly remand and medium security settings
- Inpatient HCV treatment (e.g. PWID with infectious complications of injecting)
- Needle Syringe Program – based treatment for PWID
- Acute HCV, including treatment of HCV reinfection
- When cost-effectiveness significantly enhanced (including generic LMIC settings)
Sofosbuvir/Velpatasvir/Voxilaprevir

GT1, treatment naïve, F0-4, 4-8 weeks

<table>
<thead>
<tr>
<th>SVR12 %</th>
<th>8 weeks (F0-3)</th>
<th>8 weeks (F4)</th>
<th>6 weeks (F0-3)</th>
<th>6 weeks (F4)</th>
<th>4 weeks (F0-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>36/36</td>
<td>31/33</td>
<td>14/15</td>
<td>13/15</td>
<td>4/15</td>
</tr>
</tbody>
</table>

SVR12 %

GT1, treatment naïve, F0-3

DAA regimens for 6 weeks

SOF + GZR/EBR: 26/30
SOF/LDV + GS-9451: 19/20
SOF/LDV + GS-9669: 19/20
SOF + DCV/BCV/ASV: 8/14
SOF/VEL/VOX: 14/15

DAA regimens for 4 weeks

GT1, treatment naïve, F0-3

<table>
<thead>
<tr>
<th>Regimen</th>
<th>SVR12 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF + GZR/EBR</td>
<td>10/31</td>
</tr>
<tr>
<td>SOF/LDV + GS-9451</td>
<td>10/25</td>
</tr>
<tr>
<td>SOF/LDV + 9451 + 9669</td>
<td>5/25</td>
</tr>
<tr>
<td>SOF + DCV/BCV/ASV</td>
<td>4/14</td>
</tr>
<tr>
<td>SOF/VEL/VOX</td>
<td>4/15</td>
</tr>
</tbody>
</table>

Future short duration studies

- Favourable sub-populations (F0-2, younger age, genotype/subtype): current DAA regimens
- Strategy studies: response-guided
- Acute/recent HCV
- New DAA combinations: SOF + GLE/PIB
- DAA + other classes: DAAs + long-acting non-oral agent
DAA regimens for 4 weeks

GT1-3, treatment naive, F0-1, RNA <2 million, <50 years (mean, 39 years), PWUD

- **SOF/LDV + RBV**: 75% (2 relapse, 2 LTFU)
- **SOF/LDV + RBV + PEG-IFN**: 94% (1 LTFU)

12/16 for SOF/LDV + RBV
15/16 for SOF/LDV + RBV + PEG-IFN
Ultra-short DAA therapy: response-guided 3 weeks

GT1b, treatment naive, F0-2, mean age 31-41 years, RNA<500 IU/mL day 2 (18/26)

SOF/LDV + ASV 6/6
SOF + DCV + ASV 6/6
SOF + DCV + SMV 6/6

Ultra-short DAA therapy: response-guided 3 weeks

GT1b, treatment naive, F0-2, mean age 31-41 years, RNA<500 IU/mL day 2 (18/26)

Acute/recent HCV: DAA regimens 6 weeks

- **SOF + RBV (HCV + HIV/HCV)**
  - 6/19
  - 32% non-response=2
  - relapse=9
  - reinfection=1
  - LTFU=1

- **SOF/LDV (HCV)**
  - 20/20
  - 77% relapse=3
  - reinfection=1
  - LTFU=2

- **SOF/LDV (HIV/HCV)**
  - 20/26

TARGET3D: Treatment of recently AcquiRed hepatitis C with the 3D regimen or GLE/PIB

Open label, multi-centre, sequential (Australia, NZ, UK)

- **Recent HCV GT1** (n=30)
- **PrOD +/- RBV 8 weeks** (n=30)
- **SVR 12**

- **Recent HCV GT1-6** (n=60)
- **GLE/PIB 6 weeks** (n=30)
- **SVR 12**
- **GLE/PIB 4 weeks** (n=30)
- **SVR 12**

**Closed to recruitment**

**Open to recruitment Sept 2017**
**REACT: A randomised study of interferon-free treatment for recently acquired hepatitis C in people who inject drugs and people with HIV co-infection**

Phase III randomised, open-label, non-inferiority trial (AUS, NZ, NA, Europe)

- **Randomised 1:1**
  - Recent HCV GT 1-6
  - Primary and reinfection (n=250)
  - Open to recruitment

- **SOF/VEL**
  - 12 weeks (n=125)
  - SVR 12

- **SOF/VEL**
  - 6 weeks (n=125)
  - SVR12
Acknowledgements

UNSW Australia
A/Prof. Jason Grebely
A/Prof. Gail Matthews
Prof. Andrew Lloyd
Dr. Behzad Hajariizadeh
Dr. Maryam Alavi
Dr. Tanya Applegate
Ms. Pip Marks
Dr. Marianne Martinello
Prof. Carla Treloar

Collaborators
Prof. Margaret Hellard (Australia)
Prof. Ed Gane (New Zealand)
Dr. Philip Bruggmann (Switzerland)
Prof. Olav Dalgard (Norway)
Prof. Julie Bruneau (Canada)
Dr. Jordan Feld (Canada)
Prof. Alain Litwin (USA)
Prof. Juergen Rockstroh (Germany)
Dr. Mark Nelson (UK)
Ms. Tracy Swan (USA)