Overview

- 2018 HCV PADO Meeting objectives and agenda
- Refresh on 2016 HCV PADO objectives and next steps
- Status of epidemic and response
- Major Progress in last two years
- Conclusions and next steps
2018 PADO HCV Meeting Objectives and expected outcomes

• To identify mid and longer-term priorities for development of paediatric formulations for HCV DAA to guide industry and relevant stakeholders

• To identify research gaps to inform approval, development and optimal use of HCV DAAs in children.

• To identify key strategies to promote access to DAA treatment among children and adolescents

• List of priority products for research and development to include (including 1 to include in GAP-f product portfolio

• Research priorities to inform development and optimal use of DAA in children

• Implementation considerations to promote mid and long term drug optimization for HCV
# Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Session Title</th>
<th>Presenter(s)</th>
</tr>
</thead>
</table>
| **8.45-9.00** | Welcome and meeting objectives  
Overview – current status | Philippa Easterbrook and Martina Penazzato (WHO)                               |
| **Session 1: Strategies for current and future priority DAA regimens** |  
9.00-9.30 | Overview of current status of ongoing paeds/adolescent treatment trials | Giuseppe Indolfi (Meyer Hospital)                                             |
| 9.30-9.45 | Overview of IP barriers and global access to key DAA regimens               | Yao Cheng (MPP)/Martin Auton (Global Fund)                                    |
| 9.45-10.15 | **Question and answers**                                                  |                                                                              |
| **Break** |                                                                 |                                                                              |
| **Session 2: Identifying priorities and overcoming barriers to paeds/adolescent DAA access** |  
10.30-11.15 | Regional perspective:  
* What is current status/approximate no. of adolescents/children treated with DAA regimens from region (or selected countries)?  
* What drug regimens have been used?  
* What are barriers to access and proposed next steps to address? | Webex call for regional reports |
| 11.15-12.15 | Discussion:  
1. Identifying priority products  
2. Remaining research gaps  
3. Strategies for improving paediatric access to DAA regimens. | All |
| 12.15-12.30 | Next steps and closing remarks | Philippa Easterbrook and Martina Penazzato (WHO) |
1. What are the optimal characteristics of HCV paeds drug regimens – need for a formal TPP?
   - Existing criteria: all oral, pan-genotypic, few side-effects, short-course, interferon and ribavirin-free, two DAA regimen options

2. What are the additional critical studies/trials needed to advance the agenda?
   - Are there existing opportunities that can be leveraged for paeds studies?
   - Which children need to be treated and when? esp HBV

3. What are the other critical steps needed?
   - Advocacy from group
   - Stage 1/2 of the ”Global Accelerator” for paediatric ARVs
2016 Target paediatric product profile

Treatment-naïve and experienced, cirrhotic and non-cirrhotic, HIV-coinfected GT 1-6

8 weeks

95

- High efficacy (>95%)
- Optimal safety profile (IFN/ribavirin free)
- Pan-genotypic
- Use in all patients (regardless of cirrhosis, HIV status or treatment history)
- Low cost
- High barrier to resistance
- Few drug-drug interactions
- Simplified monitoring schedule with single SVR assessment
- Easy to administer (age-specific formulation)
- Short duration of treatment
- Fixed dose combination, single pill, once daily
Next steps (2016)

• Global hepatitis strategy and 2030 goal for elimination – opportunity to consider paediatric treatment needs and options

• Convene technical paeds-hep expert group to guide and support:
  • Mapping of planned and ongoing studies
  • Prioritisation of regimens for paeds development
  • Studies on treatment outcomes with DAAs in persons <18 yrs
  • Rapid development of the best age-specific formulation

• Address research gaps:
  • Define indications for treatment in children
  • Identify predictive factors to select children who could be treated for shorter duration
  • Role of DAAs in pregnancy to prevent vertical transmission
Major testing and treatment gap

- Majority of 71 m infected persons remain undiagnosed (80%% testing gap)
- 1.76 million started HCV treatment in 2016 and 1.1 million in 2015. (75% treatment gap)

Source – WHO (Center for Disease Analysis)
Transmission:
- MTCT main route of transmission: risk is 10% in HIV-HCV co-infected mothers and 6% among HIV-negative
- Iatrogenic transmission through unsafe injections
- Horizontal transmission in adolescents

Natural history:
- Spontaneous clearance: 20%
- Histological course of chronic hepatitis C is unpredictable
- Chronic active hepatitis: 30%
- Risk of cirrhosis: 1-2%
- Few children with HCC

Countries Accounting for 80% of all Pediatric HCV Infections
- Globally, estimated 3.5 (3.1-3.9) million children 1-15 years have HCV viraemic infection
- Viraemic prevalence: 0.3% in HIC and 0.6% in LIC


Burden, Epidemiology and Natural History of Hepatitis C in Children

Transmission:
- mtct main route of transmission: risk is 10% in HIV-HCV co-infected mothers and 6% among HIV-negative
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- Horizontal transmission in adolescents

Natural history:
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Punjab India (12-17yr n=36)
Unsafe medical practices (55.5%)
IDU (11.1%)
Prior surgery (2.6%)

Globally, estimated 3.5 (3.1-3.9) million children 1-15 years have HCV viraemic infection
Viraemic prevalence: 0.3% in HIC and 0.6% in LIC

Why treat Hepatitis C infection in adolescents and children?

- Important burden of infection in some settings
- Reduce development of chronic liver disease (cirrhosis and hepatocellular carcinoma)
- Reduce horizontal transmission within families and school and among adolescents
- Give child the opportunity to grow up free of potential stigma and psychological consequences
- Reduce economic burden of managing chronic liver disease in adults and costs are lower in children
- Absence of comorbidities, better compliance, better tolerance, higher SVR rates
Global Viral Hepatitis Strategy – a roadmap to Elimination

Eliminate viral hepatitis as a major public health threat by 2030, as defined by:

- 6-10 million infections (in 2015) to 900,000 infections (by 2030)
- 1.34 million deaths (in 2015) to under 500,000 deaths (by 2030)

A global hepatitis elimination strategy must include children and adolescents.
Progress 1
Substantial price reductions for DAAs

Intensifying competition to reduce prices

Fig. 3.3. Trends in the lowest reported prices for direct-acting antivirals per 28-day supply, 2016–2017

Note: Prices as reported by DAA producers and countries in the WHO 2016 and 2017 surveys
## Hepatitis medicines can be affordable
Procurement outcomes Framework Agreements 2018-21

<table>
<thead>
<tr>
<th>Product set</th>
<th>Spend</th>
<th>Focus</th>
<th>Notes</th>
</tr>
</thead>
</table>
| 1 WHO preferred & alternative regimens | 98% ARV spend | Full scope and leverage of strategy objectives | - 30 mainstream adult & paediatric 1st, 2nd line
- "Strategic" products: TLD; TLE-400; ATV/r; DRV/r; paediatric "4-in-1" |
| 2 WHO limited/specialist use products | 2% ARV spend | Available across multiple procurement channels | - Utilize the multiagency ARV procurement working group |
| 3 Other medicines used in HIV programs | Low | Access and affordable pricing to Global Fund & other buyers | - Hepatitis B & C
- Preventative therapies
  - Isoniazid & cotrimoxazole/isoniazid/ B6
- Advanced HIV disease
  - flucytosine
  - amphotericin B
  - pergolated liposomal doxorubicin |

### Reference pricing: hepatitis C

<table>
<thead>
<tr>
<th>WHO PQ/ Global Fund ERP approved supplier</th>
<th>USD</th>
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</thead>
<tbody>
<tr>
<td>daclatasvir 30mg tablet 28</td>
<td>12</td>
</tr>
<tr>
<td>daclatasvir 60mg tablet 28</td>
<td>14</td>
</tr>
<tr>
<td>sofosbuvir 400mg tablet 28</td>
<td>20</td>
</tr>
<tr>
<td>sofosbuvir + daclatasvir 400+60mg tablet 28 day co-blister</td>
<td>70</td>
</tr>
<tr>
<td>sofosbuvir/ledipasvir 400mg/90mg tablet 28</td>
<td>65</td>
</tr>
</tbody>
</table>

## Progress 2

### WHO recommendations on treatment of children and adolescents (2018)

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Adolescents (12-17 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No cirrhosis</strong></td>
<td>• Sofosbuvir/Velpatasvir for 12 wks or</td>
<td>• Sofosbuvir/Ledipasvir for 12 wks (GT1,4,5,6)</td>
</tr>
<tr>
<td></td>
<td>• Sofosbuvir/Daclatasvir for 12 wks or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Glecaprevir/Pibrentasvir for 8wks</td>
<td>• Sofosbuvir/Ribavirin for 12 wks (GT 2)</td>
</tr>
<tr>
<td><strong>Cirrhosis</strong></td>
<td>• Sofosbuvir/Velpatasvir for 12 wks or</td>
<td>• Sofosbuvir/Ribavirin for 24 wks (GT 3)</td>
</tr>
<tr>
<td></td>
<td>• Glecaprevir/Pibrentasvir for 12 wks or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Sofosbuvir/Daclatasvir for 24 wks</td>
<td></td>
</tr>
</tbody>
</table>
## Overview of Industry/non-industry trials

<table>
<thead>
<tr>
<th>Identifier</th>
<th>12-17 years</th>
<th>6-11 years</th>
<th>3-5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>sofosbuvir/ledipasvir ± ribavirin</td>
<td>NCT 02249182</td>
<td>Hepatology 2017</td>
<td>Hepatology 2018</td>
</tr>
<tr>
<td>sofosbuvir + ribavirin</td>
<td>NCT 02175758</td>
<td>Hepatology 2017</td>
<td>AASLD 2018</td>
</tr>
<tr>
<td>sofosbuvir/ledipasvir</td>
<td>NCT 02868242</td>
<td>El-Sayed, EASL 2018</td>
<td></td>
</tr>
<tr>
<td>sofosbuvir/velpatasvir</td>
<td>NCT 03022981</td>
<td>ongoing</td>
<td>ongoing</td>
</tr>
<tr>
<td>glecaprevir/pibrentasvir</td>
<td>NCT 03067129</td>
<td>AASLD 2018</td>
<td>(6-9 9-11) ongoing</td>
</tr>
<tr>
<td>elbasvir/grazoprevir</td>
<td>NCT 03379506</td>
<td>ongoing</td>
<td>ongoing</td>
</tr>
<tr>
<td>ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin</td>
<td>NCT 02486406</td>
<td>Hepatol Commun 2018</td>
<td>ongoing</td>
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</table>

<table>
<thead>
<tr>
<th>Identifier</th>
<th>12-17 yrs</th>
<th>6-11 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>sofosbuvir/ledipasvir or sofosbuvir + daclatasvir</td>
<td>NCT 03481036</td>
<td>Dhiman, JPGN 2019</td>
</tr>
<tr>
<td>sofosbuvir + daclatasvir</td>
<td>NCT 03080415</td>
<td>Ghaffar, J Viral Hep 2018 (8-17 yrs)</td>
</tr>
<tr>
<td>sofosbuvir + daclatasvir</td>
<td>NCT 03540212</td>
<td>ongoing</td>
</tr>
<tr>
<td>gratisovir + ribavirin</td>
<td>NCT 02985281</td>
<td>ongoing (10-17 years)</td>
</tr>
</tbody>
</table>

Source: clinicaltrial.gov Dec 2018
Sofosbuvir\textsuperscript{(nNS5B)} + daclatasvir\textsuperscript{(NS5A)}

**treatment-naïve and experienced**

**12 weeks of treatment**

- **GT4 (72.5%)**
  - GT 4+1 (27.5%)
  - 12-17 years
  - Egypt

- **GT4 (100%)**
  - 8-11 years 45%
  - 12-17 years 55%
  - Egypt

- **multiple genotypes**
  - 12-17 years
  - India

<table>
<thead>
<tr>
<th></th>
<th>SVR 12, %</th>
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</thead>
<tbody>
<tr>
<td><strong>Yakoot M, 2018</strong></td>
<td>96.7</td>
</tr>
<tr>
<td><strong>Abdel Ghaffar TY, 2018</strong></td>
<td>97.5</td>
</tr>
<tr>
<td><strong>Dhiman RK, 2018</strong></td>
<td>98</td>
</tr>
</tbody>
</table>

- 29/30
- 39/40
- 44/45*  

**EMA**

**FDA**

Sofosbuvir 400 mg (>45 Kg); 200 mg (17-45 kg) QD
daclatasvir 60 mg (>45 kg); 30 mg (17-45 kg) QD

*2 HCV GT 3 patients SOF + DAC + RBV for 24 weeks
Sofosbuvir\textsubscript{(nNS5B)} / ledipasvir\textsubscript{(NS5A)} (FDC)

**6-11 years, GT4, Egypt**

Treatment-naïve and experienced (n 3)

- SVR 12, %
  - GT4 LED/SOF, 12 weeks
  - 95%
  - 19/20

*1 patient achieved EOT response and was lost to follow up

Sofosbuvir (200 mg QD), ledipasvir (45 mg QD)

El-Shabrawi MHG, Aliment Pharmacol Ther 2018
Progress 3
Advocacy, policy and communication

ARTICLES

CONFERENCES

World Hepatitis Summit 2017
ESPGHAN 2018
PENTA 2018
ESPGHAN 2019
APASL/EASL/IAS 2019

PHARMA ENGAGEMENT

Gilead: SOF/LED and SOF/VEL
Abbvie: GLEC/PIB

• To accelerate studies on DAAs in children 3-12 years and development of age-specific formulations

COUNTRY POLICIES

Inclusion of children in testing and treatment policies: Egypt, Pakistan, Mongolia, Georgia, Myanmar, Vietnam
Unfinished Business....

- **Regulatory approval SOF/DAC:** Strategy for pursuing regulatory approval for adolescents and children
  - Consultation with BMS, EMA and FDA, and other regulatory agencies
  - Article 58

- **Guidelines:** Unify adult and paeds DAA recommendations

- **WHO PQ:** Ensuring WHO PQ of lower doses, scored SOF/DAC

- **Research agenda:**
  - Short course (8 week treatment studies with SOF/LED and SOF/DAC)
  - Long-acting options for G/P (UNITAID)
  - Meta-analysis (individual patient level) for SOF/DAC and global registry
  - Survey of country practices and barriers for paeds treatment

- **Policy and Implementation:**
  - Inclusion of paeds testing, care and treatment in national policies
  - Inclusion in-country reporting (stratification of cascade by age)
  - Training of HCWs (ECHO)
### Which DAA Regimens to prioritise?

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Pan genotypic</th>
<th>Efficacy</th>
<th>Duration (weeks)</th>
<th>Access</th>
<th>Cost</th>
<th>12-17 years SRA</th>
<th>6-11 Years SRA</th>
<th>&lt;6 years granules</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF/DAC</td>
<td>✔</td>
<td>✔</td>
<td>12/24</td>
<td>✔ ✔ ✔</td>
<td>&lt;$100</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>SOF/LED</td>
<td>X</td>
<td>✔</td>
<td>12/24</td>
<td>Some countries</td>
<td>✔</td>
<td>2019</td>
<td>✔</td>
<td></td>
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<tr>
<td>SOF/VEL</td>
<td>✔</td>
<td>✔</td>
<td>12</td>
<td>Some countries</td>
<td>2019</td>
<td>?2020</td>
<td>✔</td>
<td></td>
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<tr>
<td>G/P</td>
<td>✔</td>
<td>✔</td>
<td>8</td>
<td>X (MPP license)</td>
<td>2019</td>
<td>?2020</td>
<td>✔</td>
<td></td>
</tr>
</tbody>
</table>
### Where might we be heading? 2019-2020 HCV recommendations?

<table>
<thead>
<tr>
<th>No cirrhosis</th>
<th>Adults</th>
<th>Adolescents (12-17 yrs) and (6-12 yrs)</th>
<th>Children 3-6 yrs (granules)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Sofosbuvir/Daclatasvir for 12 wks or&lt;br&gt;• Sofosbuvir/Velpatasvir for 12 wks or&lt;br&gt;• Glecaprevir/Pibrentasvir for 8wks</td>
<td>• Sofosbuvir/Daclatasvir for 8-12 wks&lt;br&gt;• Sofosbuvir/Velpatasvir for 8-12 wks&lt;br&gt;• Glecaprevir/Pibrentasvir for 8 wks</td>
<td>• Sofosbuvir/Velpatasvir for 8 wks&lt;br&gt;• Glecaprevir/Pibrentasvir for 8 wks</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>• Sofosbuvir/Velpatasvir for 12 wks or&lt;br&gt;• Glecaprevir/Pibrentasvir for 12 wks or&lt;br&gt;• Sofosbuvir/Daclatasvir for 24 wks</td>
<td>• * Sofosbuvir/Ledipasvir for 12 wks (GT1,4,5,6)</td>
<td></td>
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## Summary of Patents & Licences on Pangenotypic DAAs

None of the voluntary licences below limits the Field of Use to adults only, meaning these generic DAAs can be used in line with future paediatric approvals.

<table>
<thead>
<tr>
<th>Originator</th>
<th>Patent Expiry (() for Secondary patent</th>
<th>Voluntary Licence (VL)</th>
<th>Countries covered in each VL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOF</strong></td>
<td>Gilead</td>
<td>Gilead issued direct VLs to 14 generic manufacturers</td>
<td>105 countries</td>
</tr>
<tr>
<td></td>
<td>2024 (2028, 2032)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SOF/VEL</strong></td>
<td>Gilead</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2031 (2034)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SOF/VEL/VOX</strong></td>
<td>BMS</td>
<td>VLs issued through the MPP to 10 generic manufacturers</td>
<td>112+ countries*</td>
</tr>
<tr>
<td></td>
<td>2033 (2034)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DCV</strong></td>
<td>AbbVie</td>
<td>VL available through MPP. EOI is now open</td>
<td>95+ countries*</td>
</tr>
<tr>
<td></td>
<td>2031 (2035)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GLE/PIB</strong></td>
<td>AbbVie</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2031 (2035)</td>
<td>VL available through DNDi</td>
<td>111 countries</td>
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<tr>
<td><strong>Ravidasvir</strong> (Not yet approved)</td>
<td>Pharco</td>
<td>VL available through DNDi</td>
<td>111 countries</td>
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<tr>
<td></td>
<td>2029</td>
<td>Completed by VL through MPP</td>
<td>19+ other LMICs* including 8 countries not in DCV territory</td>
</tr>
</tbody>
</table>

*Sales outside the Territory are permitted if no granted patent is being infringed.

Key messages

• Support rapid progress and SRA submissions for SOF/VEL and G/P for >6 years, and granules for <6 years

• Plan for SRA for SOF/DAC >6 years; scored tablets
  • given widespread access to and low cost of SOF/DAC in many countries, and option to use existing adult full and half dose tablets.

• Priority countries – programme for paeds care and treatment

• Promote access to testing and inclusion of paeds in national policies and guidelines

• Advocacy (session at EASL 2019)
Increase viral hepatitis testing in children and adolescents

• Significant gaps and missed opportunities for diagnosis and documenting HBV and HCV status of children of HBV-positive parents or HCV-positive mothers.

  ▪ Prioritise testing children of all HBV or HCV positive mothers (especially if mother HIV coinfected)
  ▪ Offer testing to all children and adolescents with signs and symptoms suggestive of viral hepatitis
  ▪ Consider offering testing to all adolescents attending HIV services, STI clinics and TB clinics
  ▪ Target HCV testing to children who have had medical interventions or received blood products in countries where screening not optimal or where infection control practices suboptimal.
Acknowledgements

- Giuseppe Indolfi (Italy)
- Yao Cheng (MPP)
- Fernando Pascual (MPP)
- Martina Penazatto (WHO)
- WHO GHP team
- Regional WHO advisors/focal points in hepatitis
- Manal El-Sayed (Egypt)