5th International HIV/Viral Hepatitis Co-Infection Meeting

Addressing HBV and HCV in children and adolescents

Philippa Easterbrook
Global Hepatitis programme, World Health Organization, Geneva Switzerland

Saturday - Sunday, 20-21 July 2019
Mexico City, Mexico
Outline

- Global Hepatitis Elimination Strategy – importance to children
- **HBV**: Burden, transmission, disease progression and treatment in children
- **HCV**:
  - Burden, transmission, disease progression
  - DAA treatment trials and regulatory approval
  - Guideline recommendations
  - Research Agenda and next steps to promote access
Global Viral Hepatitis Strategy – a roadmap to Elimination

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

- **New infections**: 90% reduction by 2030
- **Deaths**: 65% reduction by 2030
- **Hepatitis B + C**: 30% reduction by 2030

### Interventions

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Indicator</th>
<th>2015 Baseline</th>
<th>2020</th>
<th>2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Hepatitis B vaccine</td>
<td>Hepatitis B vaccine coverage</td>
<td>84%</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>2 HBV PMTCT</td>
<td>Hepatitis B vaccine birth dose coverage</td>
<td>39%</td>
<td>50%</td>
<td>90%</td>
</tr>
<tr>
<td>3 Blood safety</td>
<td>Donations screened with quality assurance</td>
<td>97%</td>
<td>95%</td>
<td>100%</td>
</tr>
<tr>
<td>4 Injection safety</td>
<td>Proportion of unsafe injections</td>
<td>5%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>5 Harm reduction</td>
<td>Syringes &amp; needles distributed/PWID/year</td>
<td>27</td>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>6 Testing services</td>
<td>% HBV-infected diagnosed</td>
<td>9%</td>
<td>30%</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>% HCV-infected diagnosed</td>
<td>20%</td>
<td>30%</td>
<td>90%</td>
</tr>
<tr>
<td>Treatment</td>
<td>% diagnosed with HBV on treatment</td>
<td>8%</td>
<td>-</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>% diagnosed with HCV started on treatment</td>
<td>7%</td>
<td>-</td>
<td>80%</td>
</tr>
</tbody>
</table>
A global hepatitis elimination strategy must include children and adolescents

1.9 billion children (<15 yrs) - 27% of world's population

HIV & AIDS: Leaving no child behind

"Every child and young person deserves to live in a world free from HIV and AIDS. We are all that you have. We are your future."

Nur Syakirin Husnal "Az" Hari, 16 - Launch of the Unite for Children, Unite Against AIDS campaign in Malaysia, 2005

- Prevent mother-to-child transmission
- Provide paediatric treatment
- Prevent infection among adolescents and young people
- Protect and support children affected by viral hepatitis
0.8% of children under 5 in 2017 worldwide had chronic HBV infection

Source: London School of Tropical Medicine & Hygiene for WHO [systematic review by Cochrane centre, with modelling inferences], schematic map of the WHO regions

Transmission and HBV-Related Liver Disease Progression in children

**Outcome of HBV infection by age at infection**

- **Transmission**
  - MTCT accounts for most HBV infections in children.
  - Horizontal transmission in early childhood may account for one third of infections.
  - Transmission during surgical and dental procedures, and traditional practices.

- **Disease Progression**
  - Key determinant of chronic infection is age of infection – occurs in 90% of infected neonates vs. <5% with adult-acquired infection.
  - “Immune tolerant” phase is key feature of perinatal or early childhood acquired infection - High-replication, Low inflammation.
  - Cirrhosis in only 1-5% of HBeAg + children.
  - HCC incidence very low.
Treatment of HBV-Related Liver Disease in children

- Inconsistent recommendations across guidelines
  - Cirrhosis (compensated or decompensated)
  - Elevated ALT and detectable HBV DNA > 2000 IU/mL
- Few require treatment – majority are in immune tolerant phase

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ages for which drug is approved</th>
<th>Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon alfa-2b</td>
<td>≥1 year</td>
<td>6 million IU/m² three times a week</td>
</tr>
<tr>
<td>Peginterferon alfa-2a</td>
<td>≥3 years</td>
<td>180 μg/1.73 m² once a week</td>
</tr>
<tr>
<td>Peginterferon alfa-2b</td>
<td>Not approved</td>
<td>NA</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>≥3 years</td>
<td>3 mg/kg daily (maximum 100 mg)</td>
</tr>
<tr>
<td>Entecavir</td>
<td>≥2 years</td>
<td>10–30 kg: 0.015 mg/kg daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(maximum 0.5 mg); &gt;30 kg: 0.5 mg daily</td>
</tr>
<tr>
<td>Adefovir</td>
<td>≥12 years</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
<td>≥2 years*</td>
<td>300 mg daily</td>
</tr>
<tr>
<td>Tenofovir alafenamide</td>
<td>≥12 years</td>
<td>25 mg daily</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>Not approved</td>
<td>NA</td>
</tr>
</tbody>
</table>
Burden, Epidemiology and Transmission of Hepatitis C in Children

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

Transmission:

- MTCT main route of transmission: risk is 10% in HIV-HCV co-infected mothers and 6% among HIV-negative
- Horizontal transmission due to unsafe medical practices (LMICs) or injecting drug use in adolescents

Disease Progression:

- Spontaneous clearance: 20%
- Usually a mild disease in childhood
  - Risk of cirrhosis: 1-2%
  - Few children with HCC
- Histological course of chronic hepatitis C is unpredictable
- Liver fibrosis increases with age and duration


# FDA and EMA Approved DAA Regimens for treatment of Adolescents (12-17 years)

<table>
<thead>
<tr>
<th>Combination</th>
<th>Genotype (GT) &amp; Duration of Treatment</th>
<th>FDA-specific indications</th>
<th>EMA-specific indications</th>
</tr>
</thead>
</table>
| **sofosbuvir/ledipasvir** (FDC 400/90 mg) 400/90 mg/day | GT 1, 4, 5, 6: **12 wks**  
GT 1, treat-ex., cirrhosis: **24 wks** | 12-17 yrs or ≥ 35 kg   | GT 3: **24 wks with ribavirin**  
GT 1, treat-naïve, HCV RNA < 6x10⁶: **8 weeks** |
| **sofosbuvir + ribavirin**  
SOF: 400 mg/day; RBV: 15 mg/Kg/day | GT 2: **12 wks**  
GT 3: **24 wks** | 12-17 yrs or ≥ 35 kg |                  |
| **glecaprevir/pibrentasvir** (FDC 100/40 mg) 300/120 mg/day | all GTs: **8 wks**  
all GTs, cirrhosis: **12 wks**  
GT 3 treat-ex: **16 wks** | ≥12 yrs or ≥ 44 kg | ≥12 yrs |
Key Regulatory approval studies in adolescents

**Sofosbuvir**ₙ NSTB / **ledipasvir**ₙ NSSA (FDC)

12-17 years, GT1, treatment-naïve and experienced

- 12 weeks
  - Overall: 98/100
  - Treatment naïve ± cirrhosis: 78/80
  - Treatment experienced no cirrhosis: 20/20

**Sofosbuvir**ₙ NSTB + **ribavirin**

12-17 years, GT2 and 3 treatment-naïve and experienced

- GT2: 12 weeks; GT3 24 weeks
  - Overall*: 98/100
  - GT2: 51/52
  - GT3*: 38/39

**Glecaprevir**ₚI / **pibrentasvir**ₙ NSSA (FDC)

12-17 years, HCV GT1-6, cirrhotic and non-cirrhotic, ± HIV co-infection

- Overall: 100
- GT1: 100
- GT2: 100
- GT3: 100
- GT4: 100
- HIV-1 co-infected: 100

Balistreri WF, Hepatology 2017; Murray K, Hepatology 2018; Schwarz KB, AASLD 2018, Jonas MM, AASLD 2018
And still to come for adolescents…….

**Sofosbuvir**<sub>(nNS5B)</sub> / **velpatasvir**<sub>(NS5A)</sub> (FDC)

NCT 02249182, industry-driven trial

**3-17 years, GT1-6, treatment-naïve and experienced**

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**Sofosbuvir**<sub>(nNS5B)</sub> + **daclatasvir**<sub>(NS5A)</sub>

**treatment-naïve and experienced**

**12 weeks of treatment**

<table>
<thead>
<tr>
<th>Week 0</th>
<th>Week 12</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF/VEL</td>
<td>SOF/VEL</td>
<td>SOF/VEL</td>
</tr>
</tbody>
</table>

**SVR 12, %**

<table>
<thead>
<tr>
<th>GT4 (72.5%)</th>
<th>GT4 (100%)</th>
<th>multiple genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Egypt</strong></td>
<td><strong>Egypt</strong></td>
<td><strong>India</strong></td>
</tr>
<tr>
<td><strong>12-17 years</strong></td>
<td><strong>12-17 years</strong></td>
<td><strong>12-17 years</strong></td>
</tr>
<tr>
<td>96.7</td>
<td>97.5</td>
<td>98</td>
</tr>
</tbody>
</table>

\[29\] \[30\] \[39\] \[40\] \[44\] \[45^*\]

\[Yakoot M, 2018\] \[Ghaffar TY, 2018\] \[Dhiman RK, 2018\]
### Comparison of the recommendations for treatment of chronic HCV infection in children and adolescents from five international guidelines

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Who to offer treatment</strong></td>
<td>12-17 years&lt;sup&gt;§&lt;/sup&gt;</td>
<td>&gt; 3 years&lt;sup&gt;§§&lt;/sup&gt;</td>
<td>&gt;12 years&lt;sup&gt;§&lt;/sup&gt;</td>
<td>all children&lt;sup&gt;§&lt;/sup&gt;</td>
<td>--</td>
<td>advanced liver disease</td>
</tr>
<tr>
<td><strong>Treatment deferral</strong></td>
<td>&lt;12 years</td>
<td>3-12 years</td>
<td>&lt;12 years</td>
<td>&lt;12 years</td>
<td>--</td>
<td>-</td>
</tr>
<tr>
<td><strong>SOF/LED&lt;sup&gt;§&lt;/sup&gt;</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>SOF/RBV&lt;sup&gt;§&lt;/sup&gt;</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>--</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>interferon-based regimens should no longer be used</td>
<td>only if DAAs are available</td>
<td>GT 2 or 3 infections can be treated with other regimens approved for adults</td>
<td>only if DAAs are available</td>
<td>no recommendation</td>
<td>guideline developed in IFN era</td>
</tr>
</tbody>
</table>

<sup>§</sup> according to FDA/EMA approvals; <sup>§</sup> independently of HCV-related liver disease severity
Initial data from regulatory approval studies in children <12 yr

Sofosbuvir$_{(nN5B)}$/ ledipasvir$_{(NS5A)}$ (FDC)

NCT 02249182, industry-driven trial

12 weeks of treatment

<table>
<thead>
<tr>
<th></th>
<th>12-17 years</th>
<th>6-11 years</th>
<th>3-5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR 12%</td>
<td>98/100</td>
<td>91/92</td>
<td>33/34</td>
</tr>
</tbody>
</table>

Indolfi and Easterbrook, Lancet Gastro Hepatol 2019

Sofosbuvir$_{(nN5B)}$ + ribavirin

NCT 02175758, industry-drive trial

GT2:12 weeks; GT3 24 weeks of treatment

<table>
<thead>
<tr>
<th></th>
<th>12-17 years</th>
<th>6-11 years</th>
<th>3-5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR 12%</td>
<td>98/52</td>
<td>41/41</td>
<td>12/13</td>
</tr>
</tbody>
</table>

Balistreri WF, Hepatology 2017; Murray K, Hepatology 2018; Schwarz KB, AASLD 2018; Wirth, Hepatology 2017; Rosenthal P, AASLD 2018
Why treat Hepatitis C infection in all children?

- Important burden of infection in some settings
- Reduce development of chronic liver disease (cirrhosis and hepatocellular carcinoma)
- DAAs are safe and effective in children and shorter course treatment option
- 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
- Improved quality of life measures (Younossi, J Viral Hep 2018)
- Absence of comorbidities, better compliance, better tolerance, higher SVR rates
### PENTA-Hep Survey in Europe

**Would you use direct-acting antivirals* active against HCV if available, for children aged**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Yes</th>
<th>No</th>
<th>Maybe</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-5 years</td>
<td>15 (42%)</td>
<td>13 (36%)</td>
<td>8 (22%)</td>
</tr>
<tr>
<td>6-10 years</td>
<td>28 (78%)</td>
<td>7 (19%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>11-18 years</td>
<td>34 (94%)</td>
<td>2 (6%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*survey distributed in 2017 Indolfi on behalf of the PENTAHep Study Group, J Viral Hep 2019
## Advocacy, policy and communication

### ARTICLES

<table>
<thead>
<tr>
<th>Title</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis in children and adolescents 1</td>
<td>Hepatitis B virus infection in children and adolescents</td>
</tr>
<tr>
<td>Hepatitis C virus infection in children and adolescents</td>
<td></td>
</tr>
</tbody>
</table>

### CONFERENCES

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

### COUNTRY POLICIES

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

### 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*
Paediatric Drug Optimisation (PADO) and Global Accelerator for Paediatric Formulations (GAP-f)

- To identify mid and longer-term priority HCV DAA products for development and paediatric formulations to guide industry and relevant stakeholders
- To identify research gaps to inform development and optimal use of DAAs in children.
- To identify key strategies to promote access to DAA treatment among children and adolescents
## 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 yrs formulation (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>
</tr>
<tr>
<td>SOF/LED</td>
<td>✗</td>
<td>✔️</td>
<td>12/24</td>
<td></td>
<td></td>
<td>✔️</td>
<td>2019</td>
<td>✔</td>
</tr>
<tr>
<td>SOF/VEL</td>
<td>✔️</td>
<td>✔️</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td>2019</td>
<td>?2020</td>
</tr>
<tr>
<td>G/P</td>
<td>✔️</td>
<td>✔️</td>
<td>8</td>
<td></td>
<td></td>
<td>✔️</td>
<td></td>
<td>?2020</td>
</tr>
</tbody>
</table>
Next Steps

• Children must not be left behind with Global hepatitis response
• Inclusion of children in national **testing/treatment guidelines**
• **Encourage champion countries** with higher burden to promote testing and treatment in children: Egypt, China, Pakistan, Mongolia, India, Nigeria
• Inclusion of children in global cascade reporting and no treated
• **Accelerate studies on DAAs in children 3-12 years** with age-specific formulation
• Addressing **barriers to hepatitis B birth dose vaccination**

**Addressing Research gaps:**
- Define indications for HBV treatment in children;
- Evaluated diagnostic performance of NITs for staging
- Identify predictive factors to select children who could be treated for shorter duration;
- Role of DAAs in pregnancy to prevent vertical transmission

**WHO 2017 testing guidelines**
- 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 in children who have had medical interventions or received blood products in countries where screening not optimal or where infection control practices suboptimal.
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