Web Annex 6. Decision-making table, PICO question on children and adolescents

In: Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection

July 2018
Acknowledgement

The World Health Organization (WHO) wishes to express its appreciation to the following individuals, who contributed to the development of this document: Marc Bulterys, WHO, Geneva, Switzerland; Roger Chou, Oregon Health and Science University, Portland, United States of America (USA); Philippa Easterbrook, WHO, Geneva, Switzerland.
### PICO question 1a and 2a: ADOLESCENTS AND CHILDREN

<table>
<thead>
<tr>
<th>When to start?</th>
<th>Which drug to use?</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the optimal timing to start treatment for chronic hepatitis C infection in adolescents and children?</td>
<td>Which DAA regimen should be used for treatment of chronic hepatitis C infection in adolescents and children?</td>
</tr>
</tbody>
</table>

#### PICOT1a question
- **Population:** adolescents (12–18 years) and children (3–12 years) from 3 to 18 years with chronic hepatitis C infection
- **Intervention:** treatment in adolescents only >12 years
- **Comparison:** initiation of treatment using direct-acting antiviral (DAA)- or interferon (IFN)-based regimen in all adolescents and children >3 years
- **Outcomes:** viral cure (sustained virological response [SVR]12), adverse events, discontinuation, drug resistance, clinical outcomes, quality of life, pharmacokinetic (PK) equivalence, transmission, costs, cost-effectiveness

#### PICOT2a question
- **Population:** adolescents and children from 3 to 18 years with chronic hepatitis C infection
- **Intervention:** initiation of treatment using specific DAA-based regimens
- **Comparison:** treatment using non-DAA IFN-based regimens
- **Outcomes:** viral cure (SVR12), adverse events, discontinuation, drug resistance, clinical outcomes, quality of life, PK equivalence, transmission, costs, cost-effectiveness

#### Subanalysis: by specific DAA regimen

### A. BACKGROUND

#### Epidemiology and burden
- It is estimated that around 3.5 million children aged 1–19 years are living with chronic HCV worldwide. Nineteen countries account for the majority of infections.
- Mother-to-child transmission is the leading source of HCV infection in children, although other modes of acquisition may also occur, including nosocomial transmission (e.g., through blood transfusions or unsafe injections) and injecting drug use in adolescents.
- While well more than a million HCV-infected people have been treated globally, few of these are adolescents or children. There are concerns that children are being left behind in the HCV treatment revolution (as occurred with HIV antiretroviral (ARV) treatment scale up).

#### Natural history
- Around 7–20% of children will experience spontaneous viral clearance, but most HCV-infected children will become chronically infected, based on European studies (Bortolotti, 2008; European Paediatric HCV network, 2005; Casetellino, 2004).
- Progression of liver fibrosis to cirrhosis is infrequent in children (around 2–3%) and few will experience end-stage liver disease during childhood, based on prospective studies (Bortolotti, 2008). There are isolated case reports of children with cirrhosis aged as young as 3 or 4 years, and rare cases of hepatocellular carcinoma (HCC) in adolescence (Gonzalez-Peralta, 2009).
- However, hepatic fibrosis may progress during childhood: among 44 children with repeated liver biopsies in the PEDS-C trial (mean 6 years interval), around one third showed an increase in the severity of hepatic fibrosis, and the proportion with bridging fibrosis/cirrhosis doubled from 11% to 20% (Mohan, 2013).
- Groups at increased risk of more rapid disease progression include children with thalassaemia major, where hepatic iron overload contributes to progression of fibrosis (Elalfy, 2013), children with HIV coinfection (Claret-
Teruel, 2011) and childhood cancer survivors (Castellino, 2004).

- Although few children will experience end-stage liver disease during childhood, they are at risk of cirrhosis and HCC in early adulthood, given that development of liver fibrosis directly correlates with increasing age and duration of infection (Guido, 2003).

- Extrahepatic manifestations: knowledge is limited of the medium- to long-term impact of HCV-related inflammation on extrahepatic manifestations in children. Development of non-organ-specific autoantibodies and subclinical hypothyroidism are common, and present in young children (Indolfi, 2008).

- Other aspects of living with chronic HCV include the fact that the infection may confer a stigma, which can impact on quality of life.

**Current treatment options**

- Despite new DAAs for adults having been available for some time (sofosbuvir was approved in 2013), there has been significant delay in evaluating their use in treating children with chronic HCV infection and, until recently, DAAs had not been licensed for adolescent or paediatric use. The only options for treating children and adolescents were the less effective and more toxic IFN-based therapies.

- In 2017, the US Food and Drug Administration (FDA) (April) and European Medicines Agency (EMA) (June/July) approved the fixed-dose combination of sofosbuvir/ledipasvir and combination of sofosbuvir and ribavirin for use in treatment-naïve and -experienced adolescents >12 years or weighing >35 kg with chronic HCV genotypes 1, 4, 5 and 6, and genotypes 2 and 3 infection, respectively.

- For children less than 12 years, DAAs are still not licensed for use. For children aged 3–12 years, IFNs (IFN α, pegylated [PEG]-IFN α-2a and -2b) and ribavirin (RBV) are still currently the only drugs approved for the treatment of chronic HCV infection. Based on registration trials, a PEG-IFN α-2a/RBV combination was approved by EMA and FDA in December 2009 and December 2008, respectively; and PEG-IFN α-2b/RBV by EMA and FDA in March 2013 and December 2009, respectively. Children with HCV genotype 1 or 4 infection should be treated for 48 weeks and those with genotype 2 or 3 for 24 weeks.

- However, results are now also becoming available from clinical studies using DAAs in children aged 6–12 years, showing comparably high rates of sustained virological response (SVR).

- Current guidelines based on access to IFN treatment from the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition recommend that the majority of children can be followed without treatment until adulthood. IFN/RBV treatment should be considered only for the few children with persistently elevated liver enzymes and/or evidence of liver fibrosis (Mack, 2012).

- A target product profile for paediatric regimens was established at WHO Paediatric ARV Drug Optimization (PADO) meeting in December 2016 and included: acceptable safety profile; tolerability; efficacy in adult trials with SVR12 >90–95%; palatability and age-appropriate formulations.

**DRAFT RECOMMENDATIONS: [to be discussed at Guidelines Development meeting]**

<table>
<thead>
<tr>
<th>ADOLESCENTS ≥12 years</th>
<th>CHILDREN &lt;12 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>• In treatment-naive and -experienced cirrhotic and non-cirrhotic adolescents aged 12 years and above or weighing at least 35 kg with chronic hepatitis C infection we recommend:</td>
<td>• In children aged less than 12 years with chronic hepatitis C infection we recommend:</td>
</tr>
<tr>
<td>o use of sofosbuvir/ledipasvir for 12 weeks for those infected with HCV genotypes 1, 4, 5, or 6 (Strong recommendation, very low quality of evidence)</td>
<td>o deferral of treatment until aged 12 years prior to approval of DAA regimens for those in age groups less than 12 years (Conditional recommendation, very low, quality of evidence)</td>
</tr>
<tr>
<td>o use of sofosbuvir and weight-based</td>
<td>o treatment with IFN-based regimens should no longer be used (Strong)</td>
</tr>
</tbody>
</table>
ribavirin for 12 weeks for those infected with HCV genotype 2, and 24 weeks for genotype 3 (Strong
treatment, very low quality of evidence)
  ○ Treatment with IFN-based regimens should no longer be used (Strong
recommendation, very low quality of evidence)

Note: other DAA regimens can be considered following regulatory approval for use in adolescents or children.

Note: prior to approval and availability of DAAs for children aged <12 years of age, exceptional treatment with IFN + ribavirin may be
considered for those children with genotype 2 or 3 infection, and
severe liver disease. This may include children at higher risk of
progressive disease, including those with HIV coinfection,
thalassaemia major and childhood cancer survivors.
B. SUMMARY AND QUALITY OF EVIDENCE

Systematic review and meta-analysis of DAA vs PEG-IFN in adolescents and children
A systematic literature search and meta-analysis were performed using MEDLINE and Embase from 1 June 2007 to 1 June 2017.

PEG-IFN and ribavirin: eleven trials reporting on combined treatment with PEG-IFN and ribavirin were included. Overall, the efficacy of this combination therapy was higher for children infected with HCV genotypes 2 and 3 (90%) than for those infected with genotypes 1 and 4 (48%). Relapse rate, independent of genotype and treatment duration, was 6%. Treatment discontinuation was reported in 17% of the children treated. Discontinuation due to severe adverse events occurred in 2%.

DAA: two trials published as full-length articles and three as abstracts were included. The overall efficacy of the different DAA combinations tested was very high (98%). Relapse rate was low (0.7%) and no treatment discontinuation was reported.

Random-effects proportional meta-analysis for children treated with pegylated interferon and ribavirin (predominantly adolescents)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percentage (95% confidence interval)</th>
<th>Number of arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained virological response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>genotypes 1 and 4</td>
<td>48.6 (44.1–53.1)</td>
<td>11</td>
</tr>
<tr>
<td>genotypes 2 and 3</td>
<td>90.9 (84.2–95.9)</td>
<td>7</td>
</tr>
<tr>
<td>Relapse</td>
<td>6.1 (2.8–10.5)</td>
<td>10</td>
</tr>
<tr>
<td>Virological breakthrough</td>
<td>3.4 (0.8–7.7)</td>
<td>8</td>
</tr>
<tr>
<td>Treatment discontinuation</td>
<td>17.7 (6.4–33.2)</td>
<td>9</td>
</tr>
<tr>
<td>due to lack of virological response</td>
<td>14.9 (15.3–29.3)</td>
<td>9</td>
</tr>
<tr>
<td>due to an adverse event</td>
<td>2.4 (1.1–4.3)</td>
<td>11</td>
</tr>
</tbody>
</table>

Random-effects proportional meta-analysis for children treated with direct-acting antivirals (predominantly adolescents)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Proportion (95% confidence interval)</th>
<th>Number of arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained virological response</td>
<td>98.1 (96.2–99.3)</td>
<td>5</td>
</tr>
<tr>
<td>genotypes 1 and 4</td>
<td>98.2 (96.2–99.5)</td>
<td>4</td>
</tr>
<tr>
<td>genotypes 2 and 3</td>
<td>96.9 (90.9–99.8)</td>
<td>2</td>
</tr>
<tr>
<td>Relapse</td>
<td>0.7 (0.08–1.9)</td>
<td>5</td>
</tr>
<tr>
<td>Virological breakthrough</td>
<td>Not calculable</td>
<td>5</td>
</tr>
<tr>
<td>Treatment discontinuation</td>
<td>Not calculable</td>
<td>5</td>
</tr>
<tr>
<td>due to lack of virological response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>due to an adverse event</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Meta-analysis results for SVR in children infected with hepatitis C virus genotypes 2 and 3 (panel A), and 1 and 4 (panel B) treated with pegylated interferon and ribavirin

Meta-analysis results for SVR in children infected with hepatitis C virus (all genotypes) treated with direct-acting antivirals
ADDITIONAL TRIAL DATA IN ADOLESCENTS >12 YEARS

Sofosbuvir/ledipasvir with genotype 1
The use of fixed-dose combination sofosbuvir/ledipasvir was approved in children aged 1–17 years and ≥35 kg, infected with HCV genotype 1 by the FDA in April 2017, and EMA in June 2017.

Study design: this was based on an open-label study of 100 GT1 HCV-infected treatment-naive and -experienced adolescents in the UK, US and Australia. Initial PK lead-in of the first 10 patients was done to confirm the dose (90 mg ledipasvir and 400 mg sofosbuvir once daily).

Study population: the median age was 15 (range 12–17) years, median BMI 21 (range 13–37) kg/m², infected with genotype 1 (81% 1a, 19% 1b), infected by perinatal transmission (84%), rate of disease (42% no cirrhosis, 1% yes cirrhosis, 57% unknown) Balistreri et al. 2017). 80 patients were treatment-naive and 20 were treatment-experienced. One out of 42 had cirrhosis.

Results: overall, there were high rates of SVR12 (98%, 98/100 patients) (Fig. 1) and good tolerability profiles and satisfactory PK profiles. The AUCtau and Cmax for sofosbuvir, GS-331007, and ledipasvir in adolescents were within the predefined PK equivalence boundaries (50–200%) found in adults in clinical trials. Two patients did not attend the post-treatment follow-up visit after achieving end-of-treatment response and were defined as lost to follow up (LTFU). The most common adverse events were headache (27%), diarrhoea (14%) and fatigue (13%). No serious adverse effects leading to treatment discontinuation were reported. All PK parameters were within the predefined equivalence boundaries when compared to adults from phase 2 and phase 3 trials of the same medications in adults. The same trial is ongoing in children aged 3–12 years.

Fig. 1. SVR12 in adolescents with HCV GT1 treated with LDV/SOF FDC

Sofosbuvir/ribavirin with genotypes 2 + 3
The use of sofosbuvir/ribavirin was approved by the FDA for use in children aged 12–17 years and ≥35 kg, infected with HCV genotype 2 or 3 in April 2017.
**Study design:** this was based on an open-label study of the PK, safety and efficacy of sofosbuvir (400 mg) and weight-based dosing (WBD) of ribavirin in 52 treatment-naive and -experienced adolescents aged 12–17 years old (NCT 02175758) at 28 sites in Australia, Germany, Italy, New Zealand, Russia, the Russian Federation, the United Kingdom of Great Britain and Northern Ireland, and the USA (Wirth, 2017).

**Study population:** the median age was 15 (range 12–17) years, median BMI was 22 (range 16–32) kg/m², infected with genotype 2 (12%), 2b (10%), 2a/2c (4%), 4 (2%), 3a (71%), infected by vertical transmission (73%), rate of disease (42% no cirrhosis, 60% unknown as did not have an assessment of stage of liver disease).

**Results:** SVR12 was 98% in the 52 adolescents treated (Fig. 2). The single patient (GT3) who did not obtain SVR12 was LTFU but did achieve SVR4. Nausea (27%) and headache (23%) were the most common adverse events reported. More than 10% of patients also experienced upper abdominal pain, diarrhoea, asthenia and dizziness. Seven patients (19%) experienced a grade 3-4 adverse event, but none discontinued treatment due to this. A small minority experienced transient, mild reductions in haemoglobin, consistent with the toxicity profile of RBV. All PK parameters were within the predefined equivalence boundaries when compared to adults from phase 2 and phase 3 trials of the same medications in adults. The same trial is ongoing in children aged 3–12 years.

**Fig. 2.** SVR12 in adolescents with HCV GT2 and GT3 treated with SOF+RBV

**Use of SOF/LED plus RBV in adolescents** for treatment-naive non-cirrhotic hepatitis C GT3:

- In registration trial (NCT 02249182), only 2 patients with HCV genotype 3 infection were treated with SOF/LED for 12 weeks and achieved SVR12.
- The EMA EPAR for Harvoni unclear – “Harvoni can be used for some patients with genotype 3”. So apparently licensed also for adolescents with HCV genotype 3 infection even though only two have been treated so far.

**PRELIMINARY TRIAL DATA IN CHILDREN <12 YEARS**
(refer to summary document and presentation at meeting)
C. BENEFITS/HARMS

**ADOLESCENTS ≥12 years and CHILDREN <12 years**

**Benefits**
- Elimination of viral hepatitis as a public health threat in many high-burden countries will be possible only if children and adolescents can also access highly effective DAA regimens for treatment and cure.
- Highly effective DAA treatment achieves cure rates >97%. Children may have even better SVR rates than adults.
- Early treatment may prevent the development of liver-related complications.
- Cognitive functioning, educational attainment and well-being may improve, even if there are no liver-related symptoms. Both physical and psychosocial health and cognitive functioning are reduced significantly in infected children compared with children without HCV (Nydegger, 2008; Rodrigue, 2009; Younossi, 2016), and may improve with DAAs.
- Treatment would reduce horizontal transmission in childhood and adolescence before the onset of risk behaviours (injecting drug use/sexual transmission).
- Treatment would enable a child to live free of a socially stigmatizing infection.
- Adults with HCV acquired in childhood are at higher risk of cirrhosis and HCC than those who acquire infection in adulthood, as liver fibrosis development directly correlates with increasing age and duration of infection (Guido, 2003).
- There was a 26-fold increased risk of liver-related death among HCV-infected adults with childhood-acquired HCV (Omland, 2010).
- It will reduce costs – as it will avoid higher costs of care and treatment associated with more advanced liver disease in adults.
- Although the same dose is used in adolescents as for adults, dosing in children will be lower, which will reduce costs.
- Recommendation and opportunity for treatment in adolescents and children will encourage testing and case-finding.
- It will simplify general population and focused testing strategies as everyone will be eligible for testing regardless of age.
- Inclusion of the recommendation would enable treatment of adolescents to be included in health insurance cover.

**Harms**
- Some adolescents and children will be diagnosed and treated for an infection that is currently causing no symptoms, which may create anxiety.

**ADOLESCENTS >12 years for use of SOF/LED and SOF/RBV**

**Harms**
- Existing recommended regimens are not pangenotypic and therefore genotyping still required
- RBV: use of RBV-based regimen is suboptimal, requiring haematological monitoring
- RBV: unknown safety in

**CHILDREN <12 years**

**Benefits of deferral**
- Significant liver disease rare in childhood
- Therapeutic superiority of DAA regimens for all GTs and better safety profile, when compared to IFN-based regimens

---

**X Benefits clearly outweigh harms**

- Benefits and harms are balanced
- Potential harms clearly outweigh potential benefits

Are the desirable anticipated effects large?
- X No
- □ Probably
- □ Uncertain
- □ Yes
- □ Varies
pregnancy and in age group more likely to have unplanned pregnancies

- Only one IFN-free option for GT 2/3 and SOF/RBV not a good regimen for GT 3 plus cirrhosis and GT2
- Consider SOF/LED plus RBV for GT3.

**EMA European public assessment reports (EPAR)** for Harvoni unclear “Harvoni can be used for some patients with genotype 3”. So licensed also for adolescents with HCV genotype 3 infection.

- Only available and approved regimen for this age group is PEG-IFN and RBV, which has well-known toxicities (including growth deficits in children), inconvenient administration route via subcutaneous IFN injections, poor efficacy and requires long duration of treatment, i.e. 6–12 months.
- Burdensome on-therapy and after-therapy safety profile of PEG-IFN and RBV. **On-therapy side-effects** include flu-like symptoms, e.g. fever, decreased appetite, asthenia and fatigue, and haematological complications such as anaemia, leukopenia and neutropenia. Potential irreversible **after-therapy side-effects**, such as thyroid disease, diabetes, ophthalmological complications and (including growth deficits in children), impairment of growth (Wirth, 2005; Jara, 2008; Narkewicz, 2010; Kelly, 2012; Jonas, 2012) means low benefit–risk ratio for treatment in children.
- General deferral of treatment until adulthood is current norm in paediatric treatment guidelines from Europe and United States.
- Recommended deferral now only until 12 years, minimizing time for disease progression and transmission.
- Potentially avoid current need for liver biopsy with use of non-invasive tests (NITs) for staging in adolescence.

**Harms from deferral**

- Progression of liver fibrosis may occur during childhood: approximately one third of children with repeat biopsies showed an increase in severity of fibrosis and in the proportion with bridging fibrosis/cirrhosis (11–20%) (Mohan, 2013).
- In some children, development of advanced liver disease can be fast and unpredictable (Badizadegan, 1998; Bortollotti, 2008).
- Physical and psychosocial health and cognitive function of even asymptomatic HCV-infected children is significantly reduced compared with children without HCV (Nydegger, 2008; Rodrigue, 2009; Haber, 2017) and would likely benefit from early therapy.

<table>
<thead>
<tr>
<th>D. ACCEPTABILITY, VALUES AND PREFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Parental support for early treatment. Views of adolescents uncertain, but with short-course treatment likely to be highly acceptable.</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
- Children supported by their parents generally have excellent compliance with treatment.

<table>
<thead>
<tr>
<th>□ No</th>
<th>x Probably</th>
<th>□ Uncertain</th>
<th>□ Yes</th>
<th>□ Varies</th>
</tr>
</thead>
</table>

E. EQUITY, ETHICS AND HUMAN RIGHT IMPLICATIONS

Will the recommendation raise questions around equity?
With more than 1 million adults who have received new HCV treatment, it is important that children and adolescents are now able to benefit from this curative treatment as quickly as possible, and enable discontinuation of less effective and more toxic IFN-based therapies.

Are there ethical implications to this recommendation?
Ensure that children and adolescents are fully informed. The consent of parent or legal guardian and assent of adolescent or child is required.

F. RESOURCE USE AND FINANCIAL IMPLICATIONS

- The costs are decreasing in high-, middle- and low-income countries (cite WHO HCV Treatment access report 2018 for current costs)
- Costs of care and treatment in children are lower as reduced dose, fewer comorbidities, fewer cases of cirrhosis and potentially shorter treatment.
- Cost effective – as will avoid higher costs of care and treatment associated with more advanced liver disease in adults

<table>
<thead>
<tr>
<th>□ Less equitable</th>
<th>x More equitable</th>
</tr>
</thead>
</table>

Are the resources required small?

G. FEASIBILITY AND CONSTRAINTS TO IMPLEMENTATION

- Majority of those infected are undiagnosed. Very few adolescents or children are being tested and diagnosed. In a recent US study (HCV prevalence in children 0.2–0.4%, only 1 in 7 children with HCV were identified and <2% were offered treatment (Delgado-Borrego, 2012). Reasons include lack of awareness about opportunities for HCV cure among adolescents in the population, and among health-care workers.
- Few low- or middle-income countries have included testing or treatment of adolescents or children in their national guidelines.
- Low- and middle-income countries with already significant financial constraints on treatment scale up may be unwilling to extend treatment to adolescents in the initial phase of scaling up.

<table>
<thead>
<tr>
<th>□ No</th>
<th>x Probably</th>
<th>□ Uncertain</th>
<th>□ Yes</th>
<th>□ Varies</th>
</tr>
</thead>
</table>

1. RELEVANCE TO DIFFERENT SETTINGS/POPULATIONS

Are any major barriers expected for the implementation of this recommendation?
Will this recommendation be most relevant for particular settings (e.g. endemicity)?

- Relevant to all high-burden settings. About 19 countries account for 80% of the burden. Highest-burden countries for paediatric infection include Pakistan, Egypt, Nigeria, China, Russia, Indonesia and Ukraine.
- In a large number of LMICs, including those with a high HCV prevalence, almost half of the population is under 25 years of age. Therefore, even if prevalence is low, they constitute a significant proportion of the infected population.
H. DRAFT RECOMMENDATIONS:

**ADOLESCENTS ≥12 years**
- In adolescents aged 12 years and above or weighing at least 35 kg with chronic hepatitis C infection (treatment-naive and -experienced cirrhotic and non-cirrhotic) we recommend:
  - use of sofosbuvir/ledipasvir for 12 weeks for those infected with HCV genotypes 1, 4, 5 or 6 *(Strong recommendation, very low quality of evidence)*
  - use of sofosbuvir and weight-based RBV for 12 weeks for those infected with HCV genotype 2 and 24 weeks for those infected with genotype 3 *(Strong recommendation, very low quality of evidence)*
  - Treatment with IFN-based regimens should no longer be given *(Strong recommendation, very low quality of evidence)*

**CHILDREN <12 years**
- In children aged less than 12 years with chronic hepatitis C infection we recommend:
  - deferral of treatment until aged 12 years prior to approval of DAA regimens for those in age groups less than 12 years *(Conditional recommendation, very low, quality of evidence)*
  - Treatment with IFN-based regimens should no longer be given *(Strong recommendation, very low quality of evidence)*

**Note.** Prior to approval and availability of DAAs for children <12 years of age, exceptional treatment with IFN + RBV may be considered for those children with genotype 2 or 3 infection and severe liver disease. This may include children at higher risk of progressive disease, including those with HIV coinfection, thalassaemia major and childhood cancer survivors.

**Note.** Other DAA regimens can be considered following regulatory approval for use in adolescents or children.

I. STRENGTH OF RECOMMENDATION

As above, and see GRADE tables below and attached.

J. RATIONALE FOR RECOMMENDATION:

Both ADOLESCENTS ≥12 years and CHILDREN <12 years

Goal of treatment in childhood is prevention of HCV-associated liver damage and extrahepatic disease, and to achieve an HCV-free generation of children.
- On the basis of adult clinical trials of DAA regimens, there is a potential to cure paediatric HCV in the vast majority of children treated.
- Elimination of viral hepatitis as a public health threat will be possible only if adolescents and children with chronic hepatitis C can also benefit from treatment and cure. Viral eradication means that a child can live free of a socially stigmatizing infection. Will align with forthcoming US and European recommendations (AASLD/IDSA and European Society for Pediatric Gastroenterology, Hepatology and Nutrition).
- Overall benefits of treatment of all infected adolescents and children outweigh the risks, as costs continue to decrease in high-, middle- and low-income countries.

ADOLESCENTS ≥12 years or weighing at least 35 kg: SOF/LED or SOF/RBV

- Comparable outcomes in adolescents to adults in two published trials: comparable high SVR rates (98% for GT1/4; 100% for GT2 and 97% for GT3). No serious adverse events or significant laboratory abnormalities with SOF/LED and SOF/RBV.
- European Medicines Agency (EMA) and the Food and Drug Administration (FDA) approval in 2017 of two regimens for treatment of adolescents (12–17 years, weighing more than 35 kg: (fixed-dose combination SOF/LED and combination of SOF/RBV)

CHILDREN <12 years: recommendation for deferral until 12 years and not use IFN-based regimens

- Overall low efficacy, prolonged treatment duration of IFN-based treatments (24–48 weeks), and significant side-effect profile, including growth deficits that are unique to children), inconvenient administration route via subcutaneous IFN injections, and high cost.
- IFN increasingly less available, especially in LMICs
- Current approach is to defer treatment until aged 12 years or until the new highly effective short-course oral DAA regimens become available.
for GTs 1, 4, 5 and 6, and GTs 2 and 3 infections, respectively.

- SOF/LED and SOF/RBV fulfil criteria for TPP identified at PADO meeting (December 2016)
  - Acceptable safety profile
  - Tolerability
  - Efficacy SVR12 >95%

- Only a small number of children have significant liver disease that would benefit from early treatment.

K. IMPLEMENTATION CONSIDERATIONS

1. Need for adoption of 2017 WHO testing guideline recommendations for adolescents and children in national testing and treatment guidelines. As all adolescents and children, regardless of age, stage of disease, risk group, become potential candidates for treatment with approved effective DAA regimens, there is a need to scale up testing to identify undiagnosed cases.

2. Future drug development and approval

Opportunity to accelerate evaluation and approval of future paediatric drug regimens through revised EMA approach to registration of DAA regimens for paediatric use (EMA Expert meeting on the clinical investigation of medicines for the treatment of paediatric hepatitis C (www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2014/12/event_detail_001074.jsp&mid=WC0b01ac0580ff86ad), such that regimens Drugs can now be approved on the basis of phase I/II clinical studies of 30–40 children. Uncertain whether FDA will follow the same path.

Given the expected high efficacy of the multiple DAA regimens approved in adults and in development, comparative trials are unrealistic and may be unnecessary. Can extrapolate data from adult clinical trials and define what criteria should be applied in selecting the most promising regimens for treating children. Base approval on pre-authorization phase II/III clinical studies of 30–40 children, with PK and limited tolerability and efficacy data. Post-licensure and approval, safety and efficacy studies can collect longer-term and more detailed data.

3. Palatability and age-appropriate formulations need to be prioritized and developed.

L. RESEARCH GAPS

Ongoing studies with DAAs in children and adolescents with chronic HCV infection (last update August 2017)

<table>
<thead>
<tr>
<th>Combined regimens</th>
<th>Genotype</th>
<th>Identifier</th>
<th>Expected completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>glecaprevir/pibrentasvir</td>
<td>1–6</td>
<td>NCT 03067129</td>
<td>May 2022</td>
</tr>
<tr>
<td>ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin</td>
<td>1, 4</td>
<td>NCT 02486406</td>
<td>September 2019</td>
</tr>
<tr>
<td>sofosbuvir + daclatasvir</td>
<td>4</td>
<td>NCT 03080415</td>
<td>June 2018</td>
</tr>
<tr>
<td>ledipasvir/sofosbuvir + ribavirin</td>
<td>1, 4</td>
<td>NCT 02868242</td>
<td>April 2019</td>
</tr>
<tr>
<td>ledipasvir/sofosbuvir ± ribavirin</td>
<td>1, 4, 5, 6</td>
<td>NCT 02249182</td>
<td>July 2018</td>
</tr>
</tbody>
</table>
1. Sofosbuvir plus ledipasvir and weight-based RBV for use in treatment-naive non-cirrhotic genotype 3 infection (currently only adult published data)
2. Long-term follow-up studies for 2–3 years in those treated to examine impact on growth, cognitive function, educational attainment. No long-term study (beyond 24 weeks after the end of treatment) is currently available for DAAs in children.
3. Potential shortening of treatment regimen to 8 weeks
4. Need for more IFN-free options for GT 2/3
5. Future trials should include children whose DAA regimens have failed and genotype coverage should reflect that of adult studies. Should reflect that of adult trials
6. Future studies are needed to identify the best combinations for treating adolescents and children, when to initiate treatment, and management of those with treatment failure.
7. Cost–effectiveness studies on treating children with DAAs, including acceptability and quality of life
8. Prioritization of DAA regimens for paediatric development, using a strategy of extrapolating data from adult clinical trials and then applying criteria to select the most promising regimens for treating children
9. Need for paediatric formulations (granules) for those less than 6 years
10. Address knowledge gaps in epidemiology/burden and natural history of chronic HCV infection acquired vertically or in childhood and in adolescence. These include the longer-term clinical outcomes of chronic HCV acquired vertically or in childhood and the extent of undiagnosed paediatric/adolescent HCV infection.

Note: * Egyptian children undergoing cancer chemotherapy

<table>
<thead>
<tr>
<th>Sofosbuvir + ribavirin</th>
<th>2, 3</th>
<th>NCT 02175758</th>
<th>April 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir/velpatasvir</td>
<td>1–6</td>
<td>NCT 03022981</td>
<td>December 2019</td>
</tr>
</tbody>
</table>

References


Younossi ZM, Stepanova M, Balistreri W, Schwarz KB, Murray KF, Rosenthal P et al. (2016). High efficacy and significant improvement of quality of life (QoL) in adolescent patients with hepatitis C genotype 1 (GT1) treated with sofosbuvir (SOF) and ledipasvir (LDV). Hepatology. 64(51): abstract 709. OR Hepatology. 63(1 Supplement 1): 351A–352A. Date of publication: 1 Oct 2016
## Summary of judgements

<table>
<thead>
<tr>
<th></th>
<th>Judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Problem</strong></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Probably no</td>
</tr>
<tr>
<td></td>
<td>Probably yes</td>
</tr>
<tr>
<td></td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td>varies</td>
</tr>
<tr>
<td><strong>Certainty of evidence</strong></td>
<td>Very low</td>
</tr>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>High</td>
</tr>
<tr>
<td><strong>Balance of benefits and harms</strong></td>
<td>Potential harms clearly outweigh potential benefits</td>
</tr>
<tr>
<td></td>
<td>Benefits and harms are balanced</td>
</tr>
<tr>
<td></td>
<td>Benefits clearly outweigh harm</td>
</tr>
<tr>
<td><strong>Large desirable effects</strong></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Uncertain</td>
</tr>
<tr>
<td></td>
<td>Probably</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Varies</td>
</tr>
<tr>
<td><strong>Are required resources small?</strong></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Uncertain</td>
</tr>
<tr>
<td></td>
<td>Probably</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Varies</td>
</tr>
<tr>
<td><strong>Equity</strong></td>
<td>Less equitable</td>
</tr>
<tr>
<td></td>
<td>More equitable</td>
</tr>
<tr>
<td><strong>Acceptability</strong></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Uncertain</td>
</tr>
<tr>
<td></td>
<td>Probably</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Varies</td>
</tr>
<tr>
<td><strong>Feasibility</strong></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Uncertain</td>
</tr>
<tr>
<td></td>
<td>Probably</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Varies</td>
</tr>
</tbody>
</table>