



UPDATED RECOMMENDATIONS ON
**TREATMENT OF ADOLESCENTS
AND CHILDREN WITH
CHRONIC HCV INFECTION**

POLICY BRIEF

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Updated recommendations on treatment of adolescents and children with chronic HCV infection: policy brief

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ACRONYMS AND ABBREVIATIONS

DAA	direct-acting antiviral (drug)	POC	point-of-care
DCV	daclatasvir	RCT	randomised clinical trial
FDC	fixed-dose combination	RNA	ribonucleic acid
G/P	glecaprevir/pibrentasvir	SOF	sofosbuvir
GDG	Guidelines Development Group	SOF/DCV	sofosbuvir/daclatasvir
GRC	Guidelines Review Committee	SOF/LED	sofosbuvir/ledipasvir
GT	Genotype	SOF/VEL	sofosbuvir/velpatasvir
HCV	hepatitis C virus	SVR	sustained virologic response
LMIC	low- and middle-income countries	WHO	World Health Organization
PK	pharmacokinetic		

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BACKGROUND

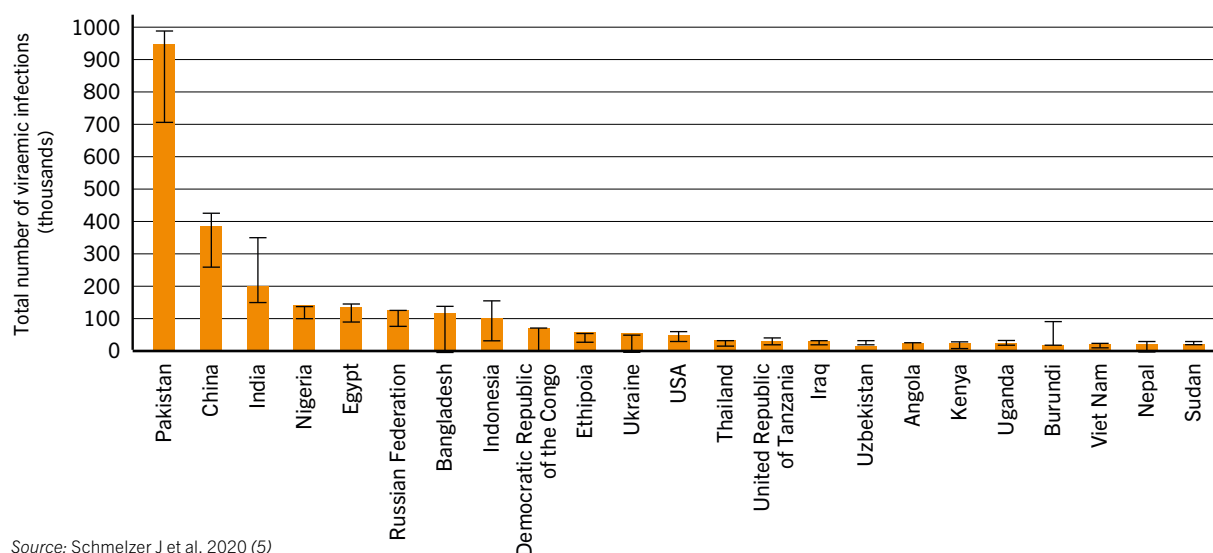
Hepatitis C virus (HCV) infection is a major public health problem. HCV infection causes chronic liver disease that leads to nearly 400 000 deaths annually. In 2019 WHO estimated that 58 million persons were chronically infected and living with hepatitis C, with a disproportionately high burden in low- and middle-income countries (LMICs) (1). Short-course, oral, curative direct-acting antiviral (DAA) regimens have transformed treatment for HCV infection in adults, who bear the greatest burden of morbidity and mortality, and now more than 10 million people have been treated since 2015 (1). The 2018 WHO HCV guidelines recommended a “treat all” approach in adults using three pangenotypic DAAs— sofosbuvir/daclatasvir (SOF/DCV), sofosbuvir/velpatasvir (SOF/VEL) and glecaprevir/pibrentasvir (G/P) (2).

Until recently there had been less attention to addressing HCV in children and adolescents, and there were no DAA regimens approved for use in children (3, 4). In 2018 there were an estimated 3.26 million children and adolescents, ages 18 years and younger, living with chronic HCV infection (5). Twenty-three countries account for 80% of this global burden, and Pakistan, China, India and Nigeria alone account for more than 50% (Fig. 1). The predominant mode of acquisition of HCV infection in children is mother-to-child transmission. Older children and adolescents may become infected via unsafe injections and poor infection prevention and control, especially in LMICs (3). Although most children with HCV infection

have asymptomatic or minimally symptomatic liver disease (6-8), recent evidence suggests that liver disease progression may begin at a young age (9). HCV infection may also decrease the quality of life of children and adolescents, with evidence of impaired psychosocial and cognitive function, and impact on the family or caregivers (10-12). Early diagnosis and treatment in adolescents and children are key to preventing long-term morbidity related to chronic hepatitis C infection (3).

Since 2018 the high rate of HCV viral clearance observed in adults with the various pangenotypic DAA regimens has also been observed among adolescents and children. This has led to approvals by key regulatory agencies, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Sofosbuvir/ledipasvir (SOF/LED) was approved for children ages three years and older in 2019, and the pangenotypic regimens G/P and SOF/VEL were approved for adolescents in 2020 and 2021, followed by G/P and SOF/VEL in 2021 in children down to 3 years of age. Although the SOF/DCV regimen is the most widely available and lowest cost pangenotypic DAA regimen in LMICs, and its safety and efficacy in children and adolescents have been reported in multiple observational studies, there is no comparable regulatory approval for this DAA combination, as the two originator companies are no longer collaborating.

FIGURE 1 Burden of chronic hepatitis C infection in children and adolescents in the 23 most affected countries



Source: Schmelzer J et al. 2020 (5)

UPDATED HCV GUIDELINES

WHO 2022 HCV guidelines, *Updated recommendations on treatment of children and adolescents and children with chronic HCV infection, and HCV simplified service delivery and HCV diagnostics* (13), provide updated, evidence-based recommendations on priority HCV-related topics, that build on the 2018 WHO *Guidelines for the care and treatment of persons diagnosed with chronic HCV infection* (2) and the 2017 WHO *Guidelines on hepatitis B and C testing* (14).

Three priority areas were addressed, in the light of key new evidence and other supporting data:

- use of DAA treatment of adolescents and children ages ≥ 3 years
- simplified service delivery (decentralization, integration and task sharing)
- HCV diagnostics – use of point-of-care (POC) HCV ribonucleic acid (RNA) viral load testing and reflex HCV RNA viral load testing.

Target audience

These guidelines are addressed primarily to national hepatitis programme managers and other policymakers in ministries of health, particularly in LMICs, who are responsible for the development of national hepatitis testing and treatment policies and guidelines. They will also serve as a reference for health care providers and paediatricians who offer and implement hepatitis testing, care and treatment for adults, adolescents and children with chronic hepatitis C virus infection.

In 2022, WHO developed new treatment recommendations that extend the 2018 “treat all” recommendation for adults with chronic HCV infection to include adolescents and children down to 3 years, and to align the existing recommended pangenotypic DAA regimens (SOF/DCV, SOF/VEL and G/P) for adults, to those for adolescents and children. This alignment is expected to simplify procurement, promote access to treatment among children in LMICs and contribute to global efforts to eliminate the disease.

This policy brief focuses on the new recommendations on treatment of adolescents and children ages ≥ 3 years with chronic HCV infection. Another policy brief addresses the new recommendations on simplified service delivery and HCV diagnostics. In 2023 all updated recommendations for hepatitis B and C will be collated into a single, consolidated guidelines on prevention, testing, care and treatment of hepatitis B and C infection.

Guidelines methodology

In accordance with the procedures established by the WHO Guidelines Review Committee (GRC), a regionally representative and multidisciplinary Guidelines Development Group (GDG) met in October 2021 to formulate the recommendations using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (15). Evidence to inform the recommendations included two commissioned systematic reviews and meta-analyses, an assessment of the overall balance of benefits and harms (at individual and population levels), a survey of health worker values and preferences, resource use, considerations of equity and human rights, and feasibility across WHO regions.

NEW 2022 RECOMMENDATIONS

Treatment of HCV in adolescents (12-17 years), older children (6-11 years) and younger children (3-5 years)

Whom to treat? **New recommendations for adolescents and children**

We recommend treatment using pangenotypic DAA regimens for all adults, adolescents and children ages 3 years and above with chronic hepatitis C infection, regardless of stage of disease:

Adults (≥18 years): *strong recommendation; moderate certainty of evidence*

Adolescents (12–17 years¹): *strong recommendation; moderate/low certainty of evidence²*

Older children (6–11 years): *strong recommendation; moderate/very low certainty of evidence²*

Younger children (3–5 years): *conditional recommendation; very low certainty of evidence*

¹ For consistency, the same age groupings as those used in the trials for regulatory submissions were used.

² Range of certainty of evidence is based on evidence for different DAA regimens

What DAA regimens to use? **New recommendations for adolescents and children**

We recommend the use of the following pangenotypic DAA regimens in adults (18 years and above), adolescents (12–17 years), older children (6–11 years) (all *strong recommendations*) and younger children (3–5 years) (*conditional recommendation*):

- **SOF/DCV¹** for 12 weeks²: *certainty of evidence: high (adults), high (adolescents and older children); very low (younger children)*
- **SOF/VEL** for 12 weeks: *certainty of evidence: high (adults), low (adolescents and older children); very low (younger children)*
- **G/P** for eight weeks: *certainty of evidence: high (adults), moderate (adolescents and older children); very low (young children).*

¹ Most widely used regimen in adults due to availability of quality-assured, low-cost generics

² In those without cirrhosis. Treatment for 24 weeks in those who are treatment-experienced or with compensated cirrhosis.

SUMMARY OF THE EVIDENCE

Systematic review

WHO commissioned a systematic review and meta-analysis of the efficacy and safety of key DAA regimens for adolescents (12–17 years), older children (6–11 years) and younger children (3–5 years) with chronic hepatitis C virus infection, using the same age groupings used in the trials for regulatory approval. The review identified 49 studies (three RCTs, 28 non-RCTs and 18 observational studies). Together, these studies reported outcomes in 1891 adolescents (35 study arms: 183 received SOF/DCV, 102 received SOF/VEL, 47 received G/P and 1686 received SOF/

LED), 472 older children (13 study arms: 73 received SOF/VEL, 56 received G/P, 34 received SOF/DCV, and 178 received SOF/LED) and 167 young children (7 study arms: 41 received SOF/VEL, 25 received G/P, and there were no study data for SOF/DCV). Findings were based on summary estimates by regimen of sustained virological response (SVR) cure rates 12 weeks after the end of treatment (SVR12) in the three age groups. Most participants were non-cirrhotic (1786, 70.6%), treatment-naïve (1825, 72.1%) and had non-GT3 infection (1453, 57.4%).

SVR12 Cure rates

Overall, SVR12 rates were high ($\geq 95\%$) in all age groups and for the key pangenotypic DAA regimens SOF/DCV, SOF/VEL and G/P as well as for SOF/LED. Exceptions were for SOF/VEL in older children (93% (86–98)) and in young children – SOF/VEL (83% (70–93)) and G/P (92% (77–100)). The lower SVR12 in younger children receiving SOF/VEL was due to treatment discontinuations because of difficulties in taking the oral medication and not due to virological failure. There were no study data for SOF/DCV in young children.

Virologic cure rates (SVR12) after treatment were $\geq 95\%$ in all age groups and for all the key pangenotypic DAA regimens.

Pharmacokinetic (PK) modelling data supporting use of available adult formulations of SOF/DCV for children <12 years

There were no direct study data on the efficacy and safety of SOF/DCV in children ages 3-5 years. SOF/DCV (400 mg/60 mg) is the pangenotypic DAA regimen of choice for adults in many LMICs, as it is highly effective and widely available as low-cost generic formulations. It is recognised that the use of existing available adult daclatasvir formulations (60 mg and 30 mg) together with approved paediatric doses of sofosbuvir (SOF) (200 mg and 150 mg) would be an effective way to expand global access to HCV treatment for children.

The extrapolation of efficacy, safety and PK data from studies in adults, adolescents or older children to support paediatric drug development is a well-established practice in regulatory approvals (19,

Adverse events and treatment discontinuations

The rate of any adverse event was higher for children ages 3–5 years (72%, $n=92$) than for those ages 6–11 years (53%, $n=226$) or adolescents (50%, $n=318$), but serious adverse events and treatment discontinuations were uncommon ($<1\%$), except in younger children (7%) because of palatability issues with the oral formulation of SOF/VEL in this group.

All studies but two were classified as at low risk of bias. There were insufficient studies that reported on outcomes by cirrhosis, genotype, HIV status or treatment experience.

Quality of life assessment

Three other studies explored the impact of DAA treatment on the quality of life of children and adolescents. These studies showed improvement in health-related quality of life scores after achieving SVR12 (16-18).

20). Daclatasvir concentration data from 17 HCV-infected adolescents receiving SOF/DCV (400 mg/60 mg once daily) who participated in a PK study in Egypt (21) were used in a predictive model of DCV exposure in children less than 12 years of age and weighing 10 to <35 kg, using existing adult 60 mg and 30 mg doses of DCV. The aim was to determine the lowest body weight at which children could be treated using these doses. Overall, the data suggest that it should be possible to use the existing adult dose of SOF/DCV (400 mg/60 mg) in children down at least to 25 kg and a half dose (200 mg/30 mg) for those weighing 14–25 kg and potentially down even to 10 kg (22). Two complementary studies assessed SOF pharmacokinetics in children relative to adults to establish appropriate dosing in children (23, 24). Overall, exposures were comparable to those observed in adults. Two efficacy, safety and PK studies of SOF/DCV among children <12 years of age are planned in Egypt and Cambodia to confirm this dosing in young children.

Values, preferences and acceptability survey

An online survey (August to September 2021) assessed preferences and acceptability among paediatricians treating HCV-infected children and adolescents. The survey questions addressed which children to treat and prioritize and which DAA regimens to use. Among the 142 survey respondents, 94 had treated HCV-infected children or adolescents in the preceding three years. The majority (94%) reported strong support for treating (defined as very likely or likely to treat) adolescents (ages 12–17 years), and 81% expressed support for treating those ages 6–11 years. Slightly less (at 60%) supported treating children ages 3–5 years. The most common reasons cited for not treating younger age groups

included: the chance of spontaneous clearance (27%), slower disease progression and asymptomatic disease in early childhood (24%), limited clinical trial data (15%), lack of country drug approvals and registration for DAA regimens in younger age groups (22%) and difficulties with administering medication to young children (12%). The most commonly used DAA regimens for treatment across all age groups among 82 health care workers in mainly high and middle income countries, who reported recent treatment experience were: SOF/LED (52% for adolescents and 28% for older children); SOF/VEL (32% for adolescents and 20% for older children); and G/P (23% for adolescents and 10% for older children). The main reason for the choice of drug, cited by 95% of respondents, was availability of the drug at the respondents' facilities.



RATIONALE FOR THE RECOMMENDATIONS

Whom to treat?

Rationale for **strong** recommendation to treat all adolescents (12-17 years) and children (6–11 years) and **conditional** recommendation to treat younger children (3-5 years)

- **Benefits of earlier treatment in childhood and adolescence** include the following:-
 - Achieving a cure before the onset of disease progression will prevent HCV-associated liver damage and extrahepatic manifestations. Although advanced liver disease is uncommon in children and adolescents, liver fibrosis progresses over time and may lead to complications in late adolescence and/or early adulthood.
 - Other potential benefits of early treatment include avoiding stigmatization of infected children and the prevention of transmission to others, particularly among adolescents engaging in high-risk behaviours.
- **High efficacy and safety** with SVR12 rates $\geq 95\%$ in all age groups for the key pangenotypic DAA regimens already recommended for adults (SOF/DCV, G/P and SOF/VEL). This conclusion is based on high certainty of evidence for adolescents, moderate certainty for older children and very low certainty for younger children.
- **Approvals by key regulatory agencies (FDA and EMA) in 2020-2021** of pan-genotypic DAA regimens, G/P and SOF/VEL in adolescents and children down to 3 years of age.
- **Serious adverse events and treatment discontinuations were uncommon.** Although the frequency of any adverse event was higher for younger age groups (72% for children ages 3–5 years, 53% for those ages 6–11 years and 50% for adolescents), serious adverse events and treatment discontinuations were uncommon. Therefore, the benefit-to-harm ratio is very high in adolescents and older children.
- **The conditional recommendation for younger children** was based on overall low frequency of HCV-related liver disease in younger children, lack of any direct studies on use of SOF/DCV, and the lower benefit-to-harm ratio in younger children, as they experienced more treatment discontinuations due to poor palatability with some regimens.

What DAA regimens to use?

Rationale for **strong** recommendation to treat adolescents (12–17 years) and older children (6–11 years) (weighing at least 35 kg) and **conditional** recommendation to treat younger children (3-5 years) with SOF/VEL, G/P or SOF/DCV

- Direct evidence from a systematic review and meta-analysis based on use of these DAA regimens in 1891 adolescents (12–17 years) from 35 studies and 472 older children (6–11 years) from 13 studies, confirmed high efficacy, safety and tolerability, and supported by indirect evidence from adult treatment studies for all DAA regimens.
- For younger children (3-5 years) based on direct evidence from a systematic review of 167 children from 7 studies of SOF/VEL and G/P. The data to support use of SOF/DCV in younger children was based on modelled PK data in adolescents (22). This suggests that it should be possible to use the existing adult dose of SOF/DCV (400 mg/60 mg) in children at least down to 25 kg, and a half dose (200 mg/30 mg) for those weighing 14–25 kg, potentially down even to 10 kg.

TABLE 1 DURATION OF DAA TREATMENT

Age groups	Recommended pangenotypic DAA regimens			Non-pangenotypic DAA regimen (in settings with minimal GT3 infection) ²
	SOF/DCV ¹	SOF/VEL ²	G/P	SOF/LED
Adults (18 years and above)	12 weeks	12 weeks	8 weeks	12 weeks
Adolescents (12–17 years)	12 weeks	12 weeks	8 weeks	12 weeks
Older children (6–11 years)	12 weeks	12 weeks	8 weeks	12 weeks
Younger children (3–5 years)	12 weeks	12 weeks	8 weeks	12 weeks

¹ In those without cirrhosis. Treatment for 24 weeks is recommended in those who are treatment-experienced or with compensated cirrhosis. May be considered in settings where genotype 3 is known to be highly prevalent (>10%).

² For use in those with genotype 1, 4, 5, or 6 infection.

TABLE 2 DOSING OF DAA REGIMENS

Recommended pangenotypic DAA regimens			Non-pangenotypic DAA regimen (in settings with minimal GT3 infection) ¹
SOF/DCV ²	SOF/VEL	G/P ³	SOF/LED
>26 kg 400/60 mg od (film-coated tablets)	>30 kg 400/100 mg od (FDC tablet)	>45 kg 300/120 mg od (FDC tablet or 6 packets of oral pellets)	≥35 kg 90/400 mg od (FDC tablet)
14–25 kg 200 mg/30 mg ² (as single tablets, SOF preferred as smaller, 100 mg tablet)	17–29 kg 200/50 mg od (FDC tablet or granules)	30–<45 kg 250/100 mg od (5 packets of oral pellets) 20–<30 kg 200/80 mg od (4 packets of oral pellets)	17– 35 kg 45/200 mg (tablet)
	<17 kg 150/37.5 mg od (coated granules)	<20 kg 150/60mg od (3 packets of oral pellets)	<17 kg 33.75/150 mg (FDC granules packets)

FDC=fixed-dose combination

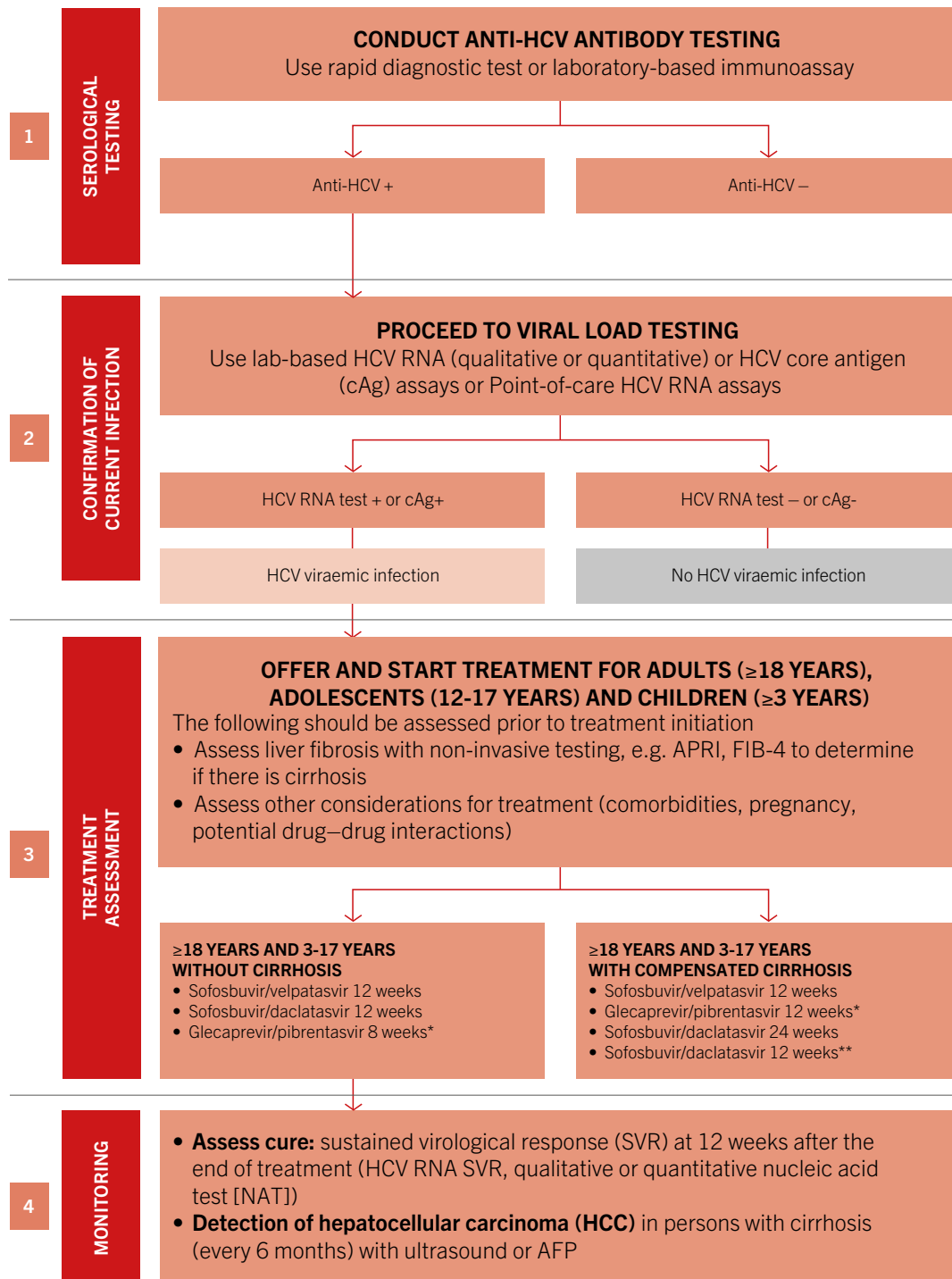
¹ For use in those with genotype 1, 4, 5, or 6 infection or where genotype 3 infection is uncommon. In the SHARED trial (in adults), an SVR with SOF/LED (400/90 mg) was observed in 261 (87%) overall, but in only 56% of those infected with HCV genotype 4r compared with 93% of those infected with genotype subtypes other than 4r. These findings do not support the use of SOF/LED as initial therapy without genotype subtyping in some regions and countries in sub-Saharan Africa.

² Dosing based on population pharmacokinetic modelling studies

³ Available as tablets (FDC) 100/40 mg or granules 50/20 mg

FIGURE 2

Summary algorithm for the diagnosis, treatment and monitoring of chronic HCV infection in adults, adolescents and children ≥ 3 years



* Persons with HCV genotype 3 infection who have received interferon and/or ribavirin in the past should be treated for 16 weeks.

** May be considered in countries where genotype distribution is known and genotype 3 prevalence is <5%.

IMPLEMENTATION CONSIDERATIONS

To be most effective in promoting access, HCV treatment programmes to reach children and adolescents need to be aligned and integrated as much as possible with programmes for adults, with pooled procurement and streamlined supply chain management.

To be most effective, HCV treatment programmes for children and adolescents need to be aligned and integrated as much as possible with programmes for adults.

1. Inclusion of case-finding, testing, care and treatment of children and adolescents in national plans and guidelines

A major constraint to implementation of these recommendations is that, currently, few LMICs have included adolescents and children in their national viral hepatitis strategic plans or their testing and treatment guidelines (4). As a result, most cases in adolescents and children remain undiagnosed and untreated. There remain significant gaps and missed opportunities for diagnosis and documenting the HCV infection status of children of infected mothers

or parents. All countries should now include HCV case-finding and testing strategies and treatment (based on the recommendations of the 2017 WHO HCV testing guidelines (14)) for adolescents and children in their national guidelines. This includes focused testing of adolescents from populations most affected by HCV infection (for example, people who inject drugs, men who have sex with men, HIV-infected persons and children of mothers with chronic HCV infection, especially if HIV-coinfected) and those with a clinical suspicion of viral hepatitis.

Testing of HCV-exposed infants could be undertaken in a range of services – child health services, immunization clinics, under-5 clinics, malnutrition services, well-child services, services for testing of hospitalized and all sick children, tuberculosis clinics, and services for orphans and vulnerable children. **Box 1** describes potential testing opportunities to improve hepatitis case-finding among infants and children. There is also a need to raise awareness among both health care workers and the public about the need to screen adolescents and children and the availability of curative treatments. The recently reported national scale-up of testing and treatment among school-age children and adolescents in Egypt has demonstrated the feasibility and acceptability of case-finding and treatment among children and their caregivers (25).

BOX 1. Testing approaches to improve hepatitis case-finding among infants and children

- Prioritize testing children of all HCV-positive mothers (especially if the mother is HCV/HIV-coinfected) through home- or facility-based testing.
- Offer testing to all children and adolescents presenting with signs and symptoms that suggest acute viral hepatitis, including anorexia, nausea, jaundice, right upper quadrant discomfort and abnormal liver function tests.
- Focus HCV testing on children who have had medical interventions or received blood products in countries with a high prevalence of hepatitis C, or where screening of blood is not routine or medical equipment is inadequately sterilized.
- Offer viral hepatitis testing or retesting to mothers and infants in immunization clinics or under-5 clinics.
- Consider offering viral hepatitis testing to all children and adolescents attending HIV services, STI clinics and tuberculosis clinics or admitted to hospitals in high prevalence regions.

2. Provision of care and treatment by non-specialists

Trained non-specialist paediatricians can treat HCV-infected children and adolescents. The few DAA-experienced HCV-infected children and adolescents and those with cirrhosis may be most appropriately managed under the supervision of a paediatric specialist. Training modules (online and in-person) are needed to support task-sharing of care and treatment by non-specialist paediatricians.

3. Resource and access considerations

Based on market-sizing estimates from the Clinton Health Access Initiative, approximately two thirds of the estimated 3.2 million HCV-infected adolescents and children (those whose weight is generally >25 or 30 kg) can use existing adult doses of the recommended DAA regimens. The remaining estimated 1.05 million HCV-infected children may require specific paediatric dosage and formulations. This includes all children in the 3–5 year age band and 80% of those ages 6–11 years (26). Countries should plan to make DAA regimens available for lower age and weight bands.

The Guidelines Development Group recognized that SOF/DCV is the most appropriate pangenotypic option to optimize access for adolescents and children in LMICs for the following reasons:

- (i) **Availability of generic products:** At present, most DAAs that could be used in children are not available as WHO pre-qualified generic products (Table 3). WHO pre-qualified DCV 30 mg is available from multiple generic suppliers and could be used in younger children. However, SOF in either 100 mg or 200 mg dosage form to pair with DCV is not yet available, and strong advocacy is needed urgently to promote development of a 100 mg SOF dosage. SOF 100 mg or 200 mg is now included on the 2022 list of products eligible for WHO pre-qualification (known as the “expression of interest”, or “EoI” list). DCV 30 mg has been included on this list since 2016.
- (ii) **Paediatric formulations for young children:** Current options include originator product formulations for G/P (pellets) and SOF/VEL (granules) or existing adult SOF/DCV 200/30 mg tablets. PK modelling results suggest that use of a dosage of SOF/DCV of 200/30 mg or half the adult dose – will provide appropriate drug exposure among younger children.
- (iii) **Cost:** SOF/DCV will continue to be substantially less expensive than other regimens, as it is available from multiple generic manufacturers at the lowest prices of any DAA regimens. The benchmark pricing is less than US\$ 100 for a WHO pre-qualified 12-week treatment course (adult doses) and at an even lower cost of US\$ 48 in Egypt and US\$ 25 in Pakistan for a locally approved 12-week treatment course (26). The originator products (G/P and SOF/VEL) are expensive and unlikely to be available at the scale needed to treat children in LMICs.
- (iv) **Potential for further cost reductions:** Alignment of adult and paediatric regimens means that programmes and manufacturers can benefit from centralized pooled procurement with larger volumes and so negotiate lower prices, as well as from streamlined supply chain management and simplified service delivery
- (v) **WHO Essential Medicines List for Children:** All the recommended DAA regimens for children and adolescents (SOF/DCV, SOF/VEL and G/P) were included in the 2021 update to the WHO Essential Medicines List for Children, which is the guide for national lists of essential medicines for children (27).

TABLE 3 DAA GENERIC SUPPLIER STATUS IN 2022

Direct acting antiviral	WHO pre-qualified suppliers
Sofosbuvir (400 mg)	Hetero, Mylan, Strides, European Egyptian Pharmaceutical Limited (Pharco)
Daclatasvir (30 mg and 60 mg)	Cipla, Hetero, Mylan, Laurus Labs
Sofosbuvir/daclatasvir FDC (400 mg/60 mg)	Cipla, Mylan
Sofosbuvir/ledipasvir FDC (400 mg/90 mg)	Mylan
Sofosbuvir/velpatasvir FDC (400 mg/100 mg)	Mylan
Sofosbuvir/velpatasvir/voxilaprevir FDC	None
Glecaprevir/pibrentasvir (300 mg/120 mg)	None

Sources: The Global Fund. "List of Antihepatitis Pharmaceutical Products. Edition: Version 24 - 11 March 2022." 2022. Accessed June 15, 2022. https://www.theglobalfund.org/media/11150/psm_productshepatitis_list_en.pdf.

World Health Organization. "The WHO List of Finished Pharmaceutical Products (FPPs) That Have Received WHO prequalification. 2022. Accessed June 15, 2022. <https://extranet.who.int/pqweb/medicines/prequalified-lists/finished-pharmaceutical-products>.

4. Service delivery for adolescents

- **Delivering adolescent-friendly services.** Providing services for adolescents requires approaches that are -focussed on and friendly to adolescents. WHO has developed standards for delivering quality services for adolescents (28). Engaging adolescents in testing for both viral hepatitis and HIV, either in health services or in the community, should be based on adolescent-friendly principles to ensure that psychological as well as medical needs are addressed. Services need to be convenient and available, offer flexible opening hours and/or walk-in or same-day appointments
- **Vulnerable adolescents.** Special considerations are needed for particularly vulnerable adolescents, those who are at higher risk of acquiring infection and have poor access to services. These include

those who are homeless, those living on the streets, orphans, boys who have sex with men, those in multiple or concurrent sexual partnerships and those who are sexually exploited or trafficked. Specific campaigns, use of social media or other Web-based approaches, and involving adolescents in identifying appropriate language may help to reach this group in some settings.

- **Age of consent.** A high legal age of consent to medical care can pose a barrier to adolescents' access to HIV and viral hepatitis testing. The age of consent for HIV testing varies from country to country. Testing services should be aware of laws and policies governing the age of consent and develop appropriate procedures based on this legal framework to ensure that children and adolescents have access to testing.

RESEARCH GAPS

Research is particularly needed in the following areas:

- direct evaluation of SOF/DCV in children ages 3–5 years and 6–11 years and <25 kg for SVR12, adverse events, tolerability and pharmacokinetics.
- country serosurvey data to inform updated estimates of prevalence and burden in adolescents and children.
- implementation research on optimal approaches for testing, case-finding and linkage to care for children and adolescents in different settings.
- follow-up studies to examine the impact of DAA treatment on growth, cognitive function, educational attainment and quality of life among children and adolescents.
- cohort studies on DAA treatment outcomes in children and adolescents with cirrhosis, that include those with prior treatment experience, genotype 3 infection and HIV coinfection.

REFERENCES

- Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021: accountability for the global health sector strategies 2016–2021: actions for impact. Geneva: World Health Organization; 2021 (<https://www.who.int/publications/item/9789240027077>, accessed 30 March 2022).
- Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. Geneva: World Health Organization; 2018 (<https://www.who.int/publications/item/9789241550345>, accessed 24 March 2022).
- Indolfi G, Easterbrook P, Dusheiko G, El-Sayed MH, Jonas MM, Thorne C et al. Hepatitis C virus infection in children and adolescents. *Lancet Gastroenterol Hepatol.* 2019;4:477-87. doi: 10.1016/s2468-1253(19)30046-9
- Malik F, Bailey H, Chan P, Collins IJ, Mozalevskis A, Thorne C et al. Where are the children in national hepatitis C policies? A global review of national strategic plans and guidelines. *JHEP Rep.* 2021;3:100227. doi: 10.1016/j.jhepr.2021.100227
- Schmelzer J, Dugan E, Blach S, Coleman S, Cai Z, DePaola M et al. Global prevalence of hepatitis C virus in children in 2018: a modelling study. *Lancet Gastroenterol Hepatol.* 2020;5:374-92. doi: 10.1016/s2468-1253(19)30385-1
- Bortolotti F, Verucchi G, Cammà C, Cabibbo G, Zancan L, Indolfi G et al. Long-term course of chronic hepatitis C in children: from viral clearance to end-stage liver disease. *Gastroenterol.* 2008;134:1900-7. doi: 10.1053/j.gastro.2008.02.082
- Iorio R, Giannattasio A, Sepe A, Terracciano LM, Vecchione R, Vegnente A. Chronic hepatitis C in childhood: an 18-year experience. *Clin Infect Dis.* 2005;41:1431-7.
- European Paediatric Hepatitis C Virus Network. Three broad modalities in the natural history of vertically acquired hepatitis C virus infection. *Clin Infect Dis.* 2005;41:45-51.
- Modin L, Arshad A, Wilkes B, Benselin J, Lloyd C, Irving WL et al. Epidemiology and natural history of hepatitis C virus infection among children and young people. *J Hepatol.* 2019;70:371-8.
- Nydegger A, Srivastava A, Wake M, Smith AL, Hardikar W. Health-related quality of life in children with hepatitis C acquired in the first year of life. *J Gastroenterol Hepatol.* 2008;23:226-30. doi: 10.1111/j.1440-1746.2007.04859.x
- Rodríguez JR, Balistreri W, Haber B, Jonas MM, Mohan P, Molleston JP et al. Impact of hepatitis C virus infection on children and their caregivers: quality of life, cognitive, and emotional outcomes. *J Pediatr Gastroenterol Nutr.* 2009;48:341-7. doi: 10.1097/MPG.0b013e318185998f
- Tehrani S, Jafari S, Yousofi J, Kiani M, Seyedin S, Khakshour A et al. Health-related quality of life (HRQOL) in children with chronic liver disease in North East Iran using PedsQL™ 4.0. *Electron Physician.* 2015;7:1214-9. doi: 10.14661/2015.1214-1219
- Updated recommendations on treatment of children and adolescents and children with chronic HCV infection, and HCV simplified service delivery and HCV diagnostics. Geneva: World Health Organization; 2022.
- Guidelines on hepatitis B and C testing. Geneva: World Health Organization; 2017 (<https://www.who.int/publications/item/9789241549981>, accessed 24 March 2022).
- WHO handbook for guideline development – 2nd ed. Geneva: World Health Organization; 2014 (<https://www.who.int/publications/item/9789241548960>, accessed 24 March 2022).
- Jonas MM, Squires RH, Rhee SM, Lin CW, Bessho K, Feiterna-Sperling C et al. Pharmacokinetics, safety, and efficacy of G/P in adolescents with chronic hepatitis C virus: Part 1 of the DORA Study. *Hepatol.* 2020;71:456-62. doi: 10.1002/hep.30840
- Younossi ZM, Stepanova M, Balistreri W, Schwarz K, Murray KF, Rosenthal P et al. Health-related quality of life in adolescent patients with hepatitis C genotype 1 treated with sofosbuvir and ledipasvir. *J Pediatr Gastroenterol Nutr.* 2018;66:112-6. doi: 10.1097/mpg.0000000000001754
- Younossi ZM, Stepanova M, Schwarz KB, Wirth S, Rosenthal P, Gonzalez-Peralta R et al. Quality of life in adolescents with hepatitis C treated with sofosbuvir and ribavirin. *J Viral Hepat.* 2018;25:354-62. doi: 10.1111/jvh.12830
- U.S. Food and Drug Administration. Chronic hepatitis C virus infection: developing direct-acting antiviral drugs for treatment guidance for industry. Silver Spring (MD): U.S. Food and Drug Administration; 2017 (<https://www.fda.gov/media/79486/download>, accessed 30 March 2022).
- U.S. Food and Drug Administration. Pediatric HIV infection: drug product development for treatment (guidance for industry). Silver Spring (MD): U.S. Food and Drug Administration; 2019 (<https://www.fda.gov/media/113319/download>, accessed 30 March 2022).
- Al-Nahari MM, Abbassi MM, Ebeid FS, Hassany M, El-Sayed MH, Farid SF. Pharmacokinetics of daclatasvir in Egyptian adolescents with genotype-4 HCV infection. *Antivir Ther.* 2020;25:101-10. doi: 10.3851/imp3357
- Cressey TR, Abbassi M, Lallemand M, Indolfi G, Al-Nahari M, Farid S et al. Effective and safe daclatasvir drug exposures predicted in children using adult formulations. *Pediatr Infect Dis J.* 2021;40:1081-6.
- Begley R, Meng A, Massetto B, Shao J, Ling J, Mathias A. Pharmacokinetics of once daily sofosbuvir or ledipasvir/sofosbuvir in HCV-infected pediatrics aged 3 to <6 years old. *Hepatology.* 2018;68:184-1354. doi: <https://aasldpubs.onlinelibrary.wiley.com/doi/full/10.1002/hep.30257>
- Rosenthal P, Schwarz K, Gonzalez-Peralta RP, Lin CH, Kelly D, Nightingale S et al. Sofosbuvir + ribavirin for 12 or 24 weeks is safe and effective in children 3 to <12 years old with genotype 2 or genotype 3 chronic hepatitis C infection [Poster 1844]. *Hepatology.* 2018;68:184-1353. doi: <https://doi.org/10.1002/hep.30257>
- Kamal E, Asem N, Hassany M, Elshishiney G, Abdel-Razek W, Said H, et al. Nationwide hepatitis C virus screening and treatment of adolescents in Egyptian schools. *Lancet Gastroenterol Hepatol.* 2022 Apr 27:S2468-1253(21)00464-7. doi: 10.1016/S2468-1253(21)00464-7.
- HCV market intelligence report 2021 and preliminary market insights. Boston: Clinton Health Access Initiative; 2021 (https://3cdmh310dov3470e6x160esb-wpengine.netdna-ssl.com/wp-content/uploads/2021/08/Hepatitis-C-Market-Report_2021-FINAL-1.pdf, accessed 24 March 2022).
- WHO model list of essential medicines - 22nd list, 2021. Geneva: World Health Organization; 2021 (<https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2021.02>, accessed 29 March 2022).
- Global standards for quality health care services for adolescents: a guide to implement a standards-driven approach to improve the quality of health care services for adolescents. Geneva: World Health Organization; 2015 (<https://apps.who.int/iris/handle/10665/183935>, accessed 24 March 2022).

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