Update on viral hepatitis B and C – testing and treatment

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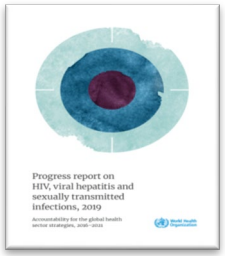
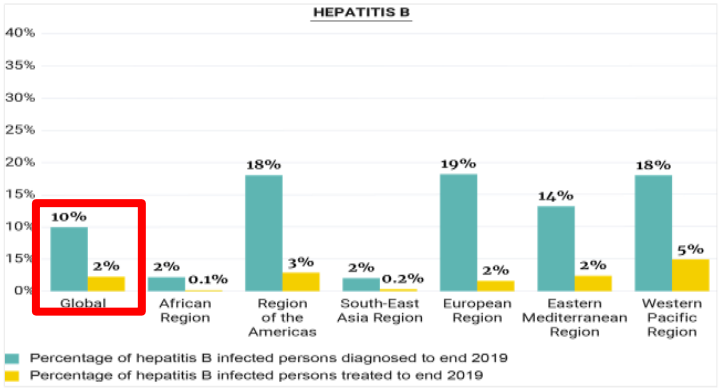
Data shows major gaps in path towards public health elimination



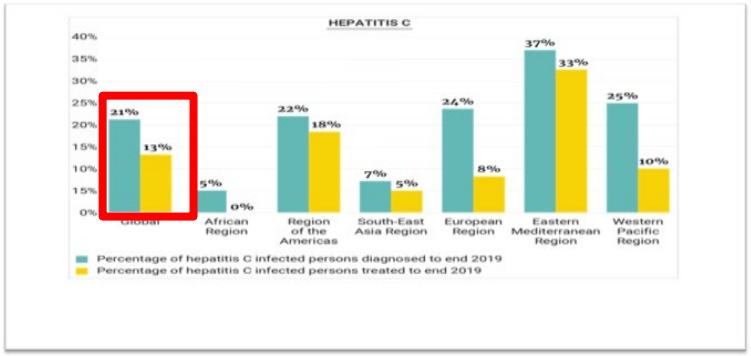
10% of estimated 296 million people with chronic HBV infection were diagnosed in 2019 with variation by regions



Data shows major gaps in path towards universal health access and public health elimination

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

21% of estimated 58 million people with chronic HCV infection were diagnosed in 2019 with variation by regions



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New Directions - Updating WHO hepatitis guidelines 2022/2023

HCV treatment: Completed

- Simplified service delivery
- Reconciling paediatric and adult DAA regime
- Re-treatment approaches and regimens

Testing: Completed

- Use of PoC viral load
- Reflex viral load
- HCV Self-testing
- Dried Blood spots

HBV treatment:

- Simplifying service delivery
- Expanding criteria for treatment (lower APRI score and HBV DNA threshold)
- Expanding criteria for use of antivirals in pregnant women
- TAF vs. TDF
- Delta virus testing and treatment

Evolution of WHO HCV Guidelines Towards Simplified HCV Service Delivery

Topic	2014	2016	2018	2022
Who to treat?			Treat All	Treat All
Genotyping	Yes	Yes	No	No
Regimens	PEG-IFN+RBV	DAAs preferred	Pan-genotypic DAAs	Pan-genotypic DAAs
	8 options - PEGIFN+RBV - SOF+RBV - SIMP or TELAP or BOCEP /PEGIFN+RBV	6 options DAAs preferred by GT or cirrhosis	3 options SOF/DAC SOF/VEL G/P PEGIFN phase out	3 options SOF/DAC SOF/VEL G/P
	SIMPLER TREATMENTS			
Age group	Adults ≥18yrs	Adults≥ 18yrs	Adults ≥18yrs and adolescents ≥12 yrs	Adults, adolescents and children≥3 yrs
			TREATMENT OF CHILDREN AND ADOLESCENTS	
Service Delivery			8 Good Practice Principles for Simplified Service	Decentralization Integration Task-shifting
			SIMPLIFIED SERVICE DELIVERY	

CHAPTER 6. SIMPLIFIED SERVICE DELIVERY FOR A PUBLIC HEALTH APPROACH TO TESTING, CARE AND TREATMENT FOR HCV INFECTION

Box 6.1. Good practice principles for health service delivery

1. **Comprehensive national planning for the elimination of HCV infection** based on local epidemiological context, existing health care infrastructure, current coverage of testing, treatment and prevention, and available financial or human resources
2. **Simple and standardized algorithms** across the continuum of care from testing, linkage to care and treatment
3. **Strategies to strengthen linkage from testing to care,** treatment and prevention
4. **Integration of hepatitis testing, care and treatment with other services** (e.g. HIV services) to increase the efficiency and reach of hepatitis services
5. **Decentralized** testing and treatment services at primary health facilities or harm reduction sites to promote access to care. This is facilitated by two approaches:
   - **5a. task-sharing,** supported by training and mentoring of health-care workers and peer workers;
   - **5b. a differentiated care** strategy to assess level-of-care needs, with specialist referral as appropriate for those with complex problems.
6. **Community engagement and peer support** to promote access to services and linkage to the continuum of care, which includes addressing stigma and discrimination
7. **Strategies for more efficient procurement and supply management** of quality-assured, affordable medicines and diagnostics
8. **Data systems to monitor the quality of individual care and coverage** at key steps along the continuum or cascade of care at the population level.

RECOMMENDATIONS

Decentralization, Integration and Task-shifting

Moving treatment and care out of speciality clinics

Decentralization:
We recommend delivery of HCV **testing** and **treatment** at peripheral health or community-based facilities, and ideally at the same site, to increase access to diagnosis, care and treatment.
These **facilities** may include primary care, harm reduction sites, prisons and HIV/ART clinics as well as community-based organizations and outreach services.

Integration:
We recommend integration of HCV **testing** and **treatment** with existing care services at peripheral health facilities.
These **services** may include primary care, harm reduction (needle and syringe programme (NSP)/opioid agonist maintenance therapy (OAMT) sites), prison and HIV/ART services.

Strong recommendation/ moderate certainty of evidence (PWID/prisoner) low (general population, PLHIV)

Task-sharing: We recommend delivery of HCV **testing, care and treatment** by trained non-specialist doctors and nurses to expand access to diagnosis, care and treatment.

Strong recommendation/ moderate certainty of evidence

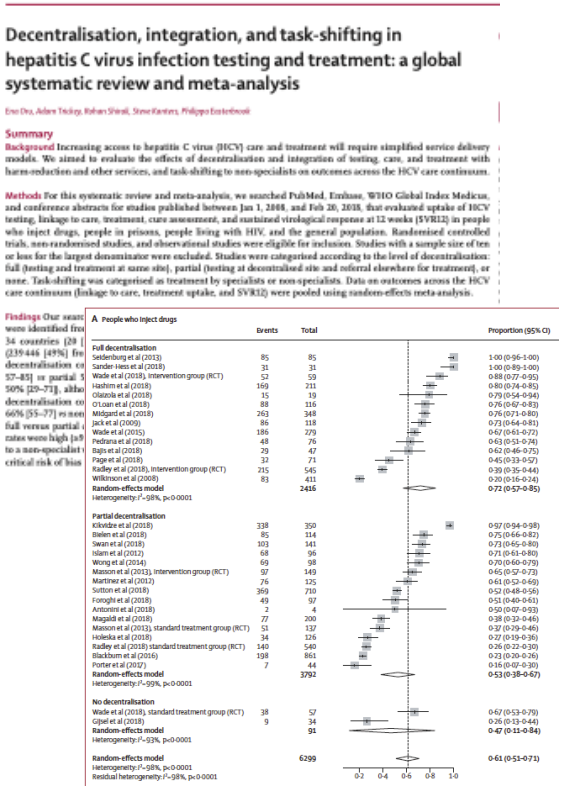
RATIONALE for Recommendations on Decentralization, Integration and Task-sharing

Evidence review

- 142 studies from 33 countries (14%) LMICs) compared full decentralization/integration vs. partial decentralization or none, and task-sharing to non-specialists.
- Increased uptake of HCV viral load testing, linkage to care and treatment among people who inject drugs and prisoners for full decentralization/integration.
- Comparable SVR12 cure rates between specialists and non-specialists across all populations and in all settings

Acceptability by end-users

- Three related surveys and a series of in-depth interviews showed strong support for fully decentralized and integrated HCV services offering testing and treatment at same community site and near to people's homes rather than in hospitals.
- Importance of a non-judgmental/non-stigmatizing approach among health care providers highlighted, especially among PWID and PLHIV.



Decentralisation, integration, and task-shifting in hepatitis C virus infection testing and treatment: a global systematic review and meta-analysis

Summary

Background Increasing access to hepatitis C virus (HCV) care and treatment will require simplified service delivery models. We aimed to evaluate the effects of decentralisation and integration of testing, care, and treatment with harm-reduction and other services, and task-shifting to non-specialists on outcomes across the HCV care continuum.

Methods For this systematic review and meta-analysis, we searched PubMed, Embase, WHO Global Index Medicus, and conference abstracts for studies published between Jan 1, 2008, and Feb 20, 2018, that evaluated uptake of HCV testing, linkage to care, treatment, cure assessment, and sustained virological response at 12 weeks (SVR12) in people who inject drugs, people in prisons, people living with HIV, and the general population. Randomised controlled trials, non-randomised studies, and observational studies were eligible for inclusion. Studies with a sample size of ten or less for the largest denominator were excluded. Studies were categorised according to the level of decentralisation: full (testing and treatment at same site), partial (testing at decentralised site and referral elsewhere for treatment), or none. Task-shifting was categorised as treatment by specialists or non-specialists. Data on outcomes across the HCV care continuum (linkage to care, treatment uptake, and SVR12) were pooled using random-effects meta-analysis.

Findings Our search were identified fro 34 countries [28 (239 446 [49%] fro decentralisation co 57–85] or partial 50% [29–71], alth decentralisation co 66% [55–77] vs non full versus partial rates were high [≥9 to a non-specialist critical risk of bias

FINDINGS Community Values and preferences for Service delivery and RNA testing and treatment

If it were possible to conduct the viral load test outside the hospital, respondents preferred:

community-based organization (45%)

primary care (GP) clinic (44%)

88% would like to conduct the initial and confirmatory tests on the **same day**

possibility to be treated more quickly (76%)

possiblity to confirm status more quickly (81%)

92% would like to conduct the initial and confirmatory tests at the **same place**

community-friendly site (60%)

convenience (70%)

85% would like to **start treatment on the same day if they had positive viral load**

avoid exposing family and friends to hepatitis C (28%)

continued follow-up from testing to treatment (27%)

92% would like to be tested and treated in the same place

convenience (34%)

continued follow-up from testing to treatment (32%)

I struggle to do doc appointments so the less places and times I have to go the better and more likely that I get them done

– Respondent XXXX

Same site means clear continuity of care, avoiding having to repeat personal story / issues and build trust with new clinician or worker

– Respondent XXXX

Differentiated care needs and approaches for viral hepatitis

Who? HCV-infected persons category	What? Care needs	Where? Site	By whom? Caregiver
Clinically well and stable	**Standard care package:** counselling, adherence support, treatment initiation and monitoring	Facility-based, including primary care or community-based settings, and mobile/outreach	Physician or nurse
Advanced liver disease or serious comorbidities, hepatocellular cancer (HCC), previous treatment failure	**Requiring more intensive clinical support and follow up:** management of liver-related complications (e.g. variceal bleed, ascites, encephalopathy, HCC treatment)	Facility-based – hospital	Physician
Mental health issues, people who inject drugs or engage in alcohol misuse, adolescents, migrants	**Requiring more intensive psychosocial/ mental health support, or intercultural and language support**	Can be facility-based or community-based, harm reduction site	Physician and counsellor/peer support

Evolution in Hepatitis C testing and diagnostic recommendations

Topic	Recommendation in 2017 testing recommendation
Who to test?	• **Focused testing** for most affected populations*, those with a clinical suspicion of chronic viral hepatitis, family members/children, and sexual partners (HBV), healthcare workers. • **General population testing**: In settings with ≥2% or ≥5% (intermediate/high) HBsAg or HCV Ab prevalence.
How to test?	• A **single** serological assay (**EIA or RDT**) that meets minimum performance standards with prompt NAT testing + linkage to care
Confirmation of HCV viraemia	• **Lab-based Nucleic acid testing (NAT) (quantitative or qualitative RNA)** or **core HCV antigen assay**, with comparable clinical sensitivity
Promoting uptake and linkage	• **Use of DBS specimens for virology ± serology** • **On-site or immediate RDT testing + same day results** • Trained peer and lay health workers • Clinician reminders to prompt provider initiated, facility-based testing • Testing as part of integrated services at a single facility

2021 and 2022 Updates

How to test - serologic
- 2021 HCV self-testing guideline

Use of POC HCV RNA NAT
- For detection of viraemia
- For test of cure

Linkage to care
- Dried blood spots (HCV serology and virology) manafacturers protocols
- Reflex viral load

RECOMMENDATIONS

2022 Recommendations on HCV diagnostics

HCV point-of-care (POC) viral load RNA testing:

- Point-of-care (POC) HCV RNA viral load assay can be an alternative approach to laboratory-based HCV RNA NAT assays to **diagnose HCV viraemic infection**.
- Point-of-care (POC) HCV RNA assays with comparable limit of detection to laboratory-based assays can be used as an alternative approach as **test of cure**.

Conditional recommendation /moderate certainty of evidence

Reflex HCV viral load testing

We recommend reflex HCV RNA testing in those with a positive HCV antibody test result as an additional key strategy to promote linkage to care and treatment.

This can be achieved either **through laboratory-based reflex HCV RNA testing using a specimen already held in the laboratory** or **clinic-based reflex testing in a health facility through immediate specimen collection** following a positive HCV antibody RDT.

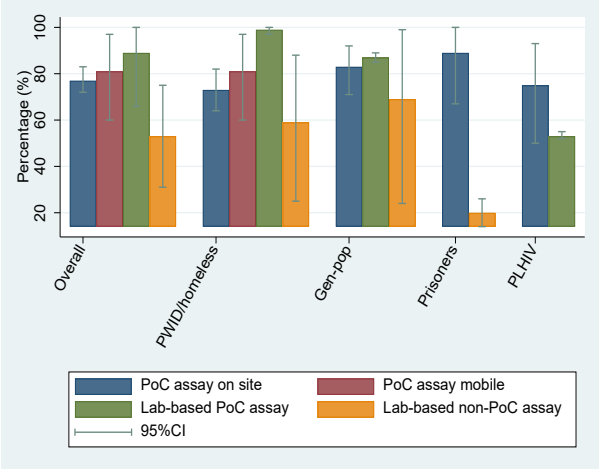
Conditional recommendation /low certainty of evidence

RATIONALE for *Conditional* Recommendation on use of HCV POC RNA assay

Evidence review

- 45 studies comprising 27 364 persons (49%) LMICs) compared POC HCV RNA assays on site with Lab-based assays.
- **Better outcomes for POC assays:** Shorter turn-around time between HCV antibody test to treatment initiation (18.5 days [95% CI: 14–53]) vs (67 days [50–67])
- Increased RNA viral load uptake (RR 1.11 [0.89–1.38] and treatment uptake (RR 1.32 [1.06–1.64]
- High sensitivity and specificity of POC assays (99% [98–99%] and 99% [99–100%) across all settings, populations, assays and specimen types

- Multi-cohort analysis of 5973 cases of detectable viraemia at SVR12. 97% with detectable viraemia at SVR12 are above 1000 IU/mL.



Other Benefits

- POC HCV RNA platforms can be used in lower levels of health facilities near where patient is receiving care.
- Opportunity for integration - POC molecular platforms are already in use for a number of other infectious diseases.

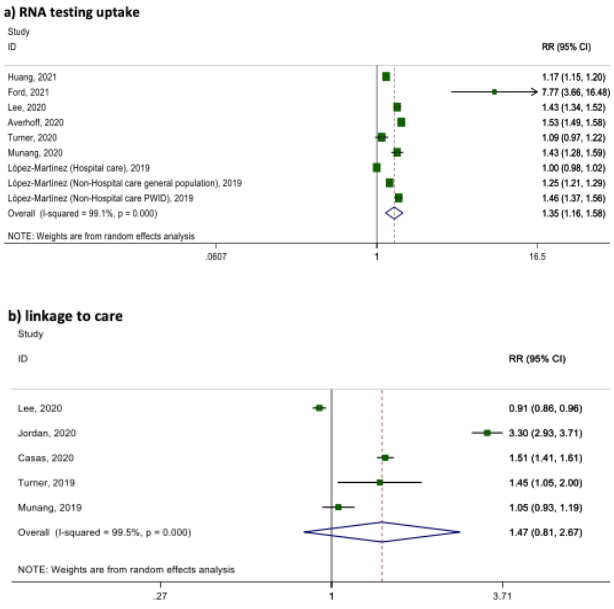
RATIONALE for Conditional Recommendations on use of Reflex viral load testing

Evidence review

- 51 studies (32 used laboratory-based reflex testing, and 19 used clinic-based reflex sample collection)
- Increased uptake of HCV viral load testing (RR 1.35 (95%CI: 1.16–1.58) and improved linkage to care (RR of 1.47 (95% CI: 0.81–2.67).

Acceptability, cost and feasibility

- Simplifies care pathway and reduces need for additional clinic visits, and time to HCV RNA
- Avoids need for additional blood draws, preferable to PWID
- Cost-saving
- Feasible to implement and potential for wide adoption to promote HCV testing and treatment uptake.
    - Lab-based reflex HCV testing already performed routinely in HICs.
    - Clinic-based reflex testing following a positive HCV antibody RDT common practice in LMICs



IMPLEMENTATION CONSIDERATIONS

HCV POC HCV RNA assays

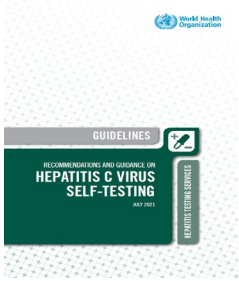
- **Strategic choice - use of lab-based vs POC NAT platforms:** will depend on characteristics of testing site. eg. (storage facilities, infrastructure, level of staff skills) and costs.
- **Priority settings for placement of HCV POC platforms** eg. PWID at harm reduction sites at high risk of loss to follow-up, where fast-tracking diagnosis can increase treatment uptake.
- **Optimal placement of a POC instrument is where testing and treatment are at the same site – a "one-stop shops"**
- **Opportunity for diagnostic integration across programmes** using **multi-disease testing platforms.** Countries with existing platforms for HIV viral load or TB testing, can consider collaboration and integration of HCV RNA testing.

HCV Reflex viral load testing

Choice of laboratory-based reflex testing or clinic-based reflex HCV RNA testing for different country contexts

- **Laboratory-based reflex testing approach** - settings with large testing volumes for HCV antibody supported by extensive sample transport networks.
- **Clinic-based reflex specimen collection approach** - settings where RDTs used and limited access to lab services, and for populations such as PWID.

WHO recommendation on HCV self-testing (2021)



HCV self-testing should be offered as an additional approach to HCV testing services

(strong recommendation, moderate-certainty evidence)

Remarks:

- HCV self-testing needs to be followed by **linkage to appropriate post-test services**, including confirmation of viraemic infection, treatment, care and referral services, according to national standards.
- **Communities, including networks of key and vulnerable populations and peer-led organizations, need to be meaningfully and effectively engaged** in developing, adapting, implementing and monitoring HCV self-testing programmes.

❑ Product pipeline

- ❑ No product with stringent regulatory approval yet
- ❑ Promising prototypes for oral and blood based HCVST

❑ Pilot projects

- ❑ STAR-Unitaid partners discussing pilot projects in 5 countries looking mainly at modalities of integration into HIVST in different populations
- ❑ FIND research – piloting distribution models and assessing effectiveness through 3 RCTS

Next Steps on HCVST

Product pipeline

- No product with stringent regulatory approval yet
- Promising prototypes for oral and blood based HCVST
- TSS published in Q1 2021 (awaiting PQ submissions and approvals)
- The assessment phase of ERPD Round 18 is underway and the outcome of the initial review will be shared with manufacturers late October-early November.

Pilot projects

- STAR-Unitaid partners discussing pilot projects in 5 countries looking mainly at modalities of integration into HIVST in different populations: India, South Africa, Cameroon, Nigeria and Vietnam.
- FIND research in Georgia, Pakistan and Malaysia – piloting distribution models and assessing effectiveness through 3 RCTS
- Georgia: CDC/WHO/FIND pilot in general population with 2 distribution models : secondary distribution in cancer screening sites and pharmacy based

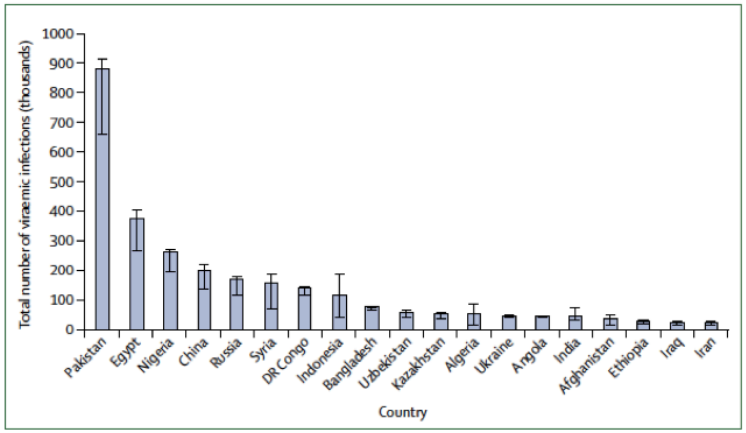
BACKGROUND

2022 Treatment Recommendations in Adolescents and Children

- Estimated 3.26 million children living with chronic HCV
- 20 countries account for 80 percent of all cases in patients 0-18 years of age
- Highest numbers living in Pakistan, China, India, Nigeria, and Egypt
- Predominant mode of acquisition of HCV infection in children is mother-to-child transmission, with iatrogenic transmission also important in some regions
- Elimination of HCV unlikely unless children are treated
- Currently only one available generic DAA with dosage form appropriate for children (adult tablets appropriate for adolescents)
- **To be effective, pediatric treatment programs will need to be aligned with adult treatment programs**
  - Pediatric dosage forms more expensive than adult tablets, especially if new formulation required (new composition, dosage form other than tablet, etc)
  - Commercial market is very small, little to no generic supplier interest

The global estimate for *viremic prevalence in the pediatric population aged 0–18* years was **0.13%** corresponding to **3.26 million** (2.07–3.90) children with HCV in 2018

Burden of chronic hepatitis C infection in children and adolescents in the 19 most affected countries



Indolfi G, et al. Hepatitis C virus infection in children and adolescents. *Lancet Gastroenterol Hepatol* 2019. Published Online April 11, 2019. http://dx.doi.org/10.1016/S2468-1253(19)30046-9

RECOMMENDATIONS

2022 Treatment Recommendations in Adolescents and Children

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

Adolescents (12–17 years[1]): *strong recommendation; moderate/low certainty of evidence*
Older children (6–11 years): *strong recommendation; moderate/very low certainty of evidence*
Younger children (3–5 years): *conditional recommendation; very low certainty of evidence*

[1] For consistency, we use the same age groupings as those used in the trials for regulatory submissions.

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/DCV**[1] for 12 weeks[2]: *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 use 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.

Reconciling DAA regimens across adults, adolescents and children

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




RATIONALE for Treatment Recommendations in Adolescents and Children

Treatment of HCV-infected adolescents and older children is highly effective and safe.
Systematic review of **49 studies** (1891 adolescents (35 studies); 472 older children (13 studies); and 167 younger children (7 studies).

- SVR12 rates ≥95% in all age groups for SOF/DCV, G/P and SOF/VEL.
- Serious adverse events and treatment discontinuations were uncommon.

Benefits of earlier treatment in childhood and adolescence include :-

- Achieving a cure before onset of disease progression will prevent HCV-associated liver damage and extrahepatic manifestations.
- Avoiding stigmatization of infected children and prevention of transmission to others

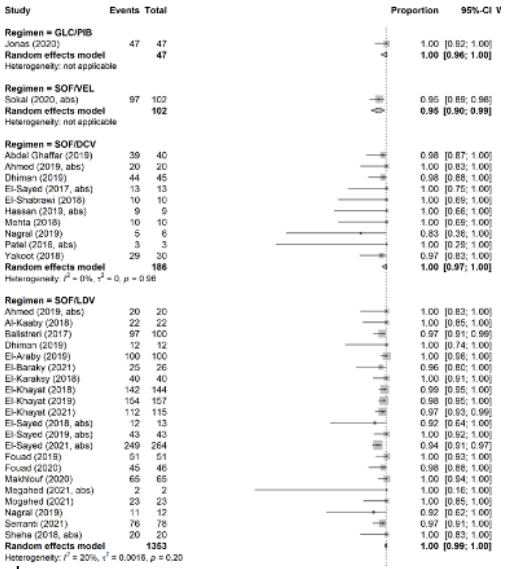
Approvals by key regulatory agencies

- DAA regimens (SOF/VEL, G/P) + SOF/LED have regulatory approval down to three years

Rationale for *conditional* recomm to treat younger children (3–5 years)

- Low frequency of HCV-related liver disease, lack of any direct studies on use of SOF/DCV, more treatment discontinuations. Very low certainty of evidence for all regimens in younger children.

- For SOF/DCV, based on extrapolation from PK modeling studies in adolescents – can use existing adult dose of SOF/DCV (400 mg/60 mg) in children >25 kg and half dose (200 mg/30 mg) for 14–25 kg.



IMPLEMENTATION CONSIDERATIONS to promote treatment for HCV infected adolescents and children

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

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. Resource and Access considerations

Availability of existing generic products
Paediatric formulations for young children
Cost and potential for further cost reductions

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

3. Service Delivery for Adolescents

- Delivery of adolescent-friendly services
- Vulnerable adolescents
- Age of consent for testing




HBV Guideline Recommendations (2015) and PMTCT update (2020)

TOPIC	RECOMMENDATION
Staging/ non-invasive test (NIT)	▪ APRI preferred NIT to assess for the presence of cirrhosis
Who to treat	▪ Decompensated cirrhosis or cirrhosis (clinical criteria or APRI score >2), regardless of ALT levels, HBeAg, or HBV DNA. ▪ No cirrhosis but persistently abnormal ALT levels +/- ongoing HBV replication, (HBV DNA >20,000 IU/mL *or* HBeAg +ve).
First line treatment	▪ Drugs with a high barrier to resistance (TDF and/or ETV and ?**TAF**). ▪ ETV in children aged 2-11 years.
Treatment failure	▪ Switch to TDF if evidence of resistance to 3TC, ETV, ADF, TBV.
Treatment discontinuation	▪ Never discontinue in persons with cirrhosis. ▪ If no cirrhosis, discontinuation on case-by-case basis (persistent HBeAg and/or HBsAg loss or undetectable HBV DNA)
Monitoring (treatment response/toxicity)	▪ *On or pre-treatment:* ALT + HBV DNA (HBsAg, HBeAg + APRI pre-treatment) annually. More frequent monitoring with cirrhosis. ▪ Assessment of baseline renal function prior to treatment initiation.
Monitoring for HCC	▪ Ultrasound + AFP every 6 months in persons with cirrhosis and/or family history of HCC.
PMTCT antiviral prophylaxis (2020)	▪ TDF prophylaxis in those with HBV DNA >200,000 IU/mL from 3rd trimester or HBeAg positive (if HBV DNA not available)

Triple Elimination of mother-to-child transmission of HIV, syphilis and HBV
Opportunity to advance the HBV EMTCT agenda

- Triple elimination of MTCT HIV, syphilis and HBV in PAHO and WPRO regions and now globally
- Multiple countries developing triple elimination framework and guidelines
- 2021 update to the “Orange book” - *Global guidance on criteria and processes for validation of elimination of mother-to-child transmission of HIV and syphilis,* to include hepatitis B