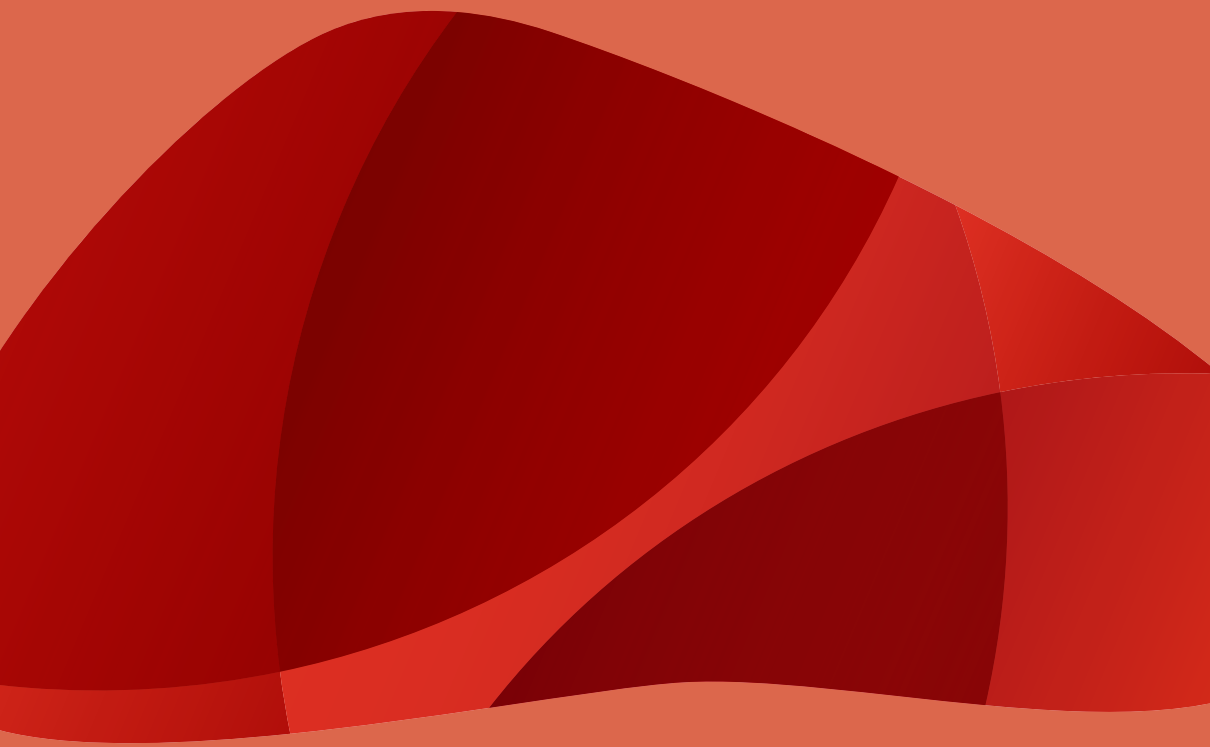
World Health Organization

UPDATED RECOMMENDATIONS ON

TREATMENT OF ADOLESCENTS AND CHILDREN WITH CHRONIC HCV INFECTION, AND HCV SIMPLIFIED SERVICE DELIVERY AND DIAGNOSTICS



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TREATMENT OF ADOLESCENTS AND CHILDREN WITH CHRONIC HCV INFECTION, AND HCV SIMPLIFIED SERVICE DELIVERY AND DIAGNOSTICS

Updated recommendations on treatment of adolescents and children with chronic HCV infection, and HCV simplified service delivery and diagnostics

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Determining the lower limit of detection required for HCV RNA viral load assay for test of cure following direct-acting antiviral-based treatment regimens: evidence from a global dataset: Jake R. Morgan (Boston University School of Public Health, USA), Sonjelle Shilton (Switzerland), Benjamin P. Linas (Boston Medical Center and Boston University School of Public Health, USA), Philippa Easterbrook (WHO headquarters), and the Limit of Detection Collaborative Group.

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The efficacy and safety of direct-acting antivirals in children and adolescents with chronic hepatitis C virus infection: Giuseppe Indolfi (University of Florence, Italy), Farihah Malik (University College London, United Kingdom), Sabrina Giometto (University of Pisa, Italy), Roger Chou (Oregon Health and Science University, USA), Philippa Easterbrook (WHO headquarters), Ersilia Lucenteforte (University of Pisa, Italy).

Effective and safe daclatasvir drug exposures predicted in children using adult formulations, a pharmaco-kinetic modelling study: Tim R. Cressey (Chiang Mai University, Thailand), Maggie Abbassi (Cairo University, Egypt), Marc Lallemant (PENTA Foundation, Italy), Giuseppe Indolfi (University of Florence, Italy), Mogeb Al-Nahari (Cairo University, Egypt), Samar Farid (Cairo University, Egypt), Martina Penazzato (WHO headquarters), Philippa Easterbrook (WHO headquarters), Manal H. El-Sayed (Ain Shams University, Egypt).

Dried blood spots protocols for HCV: Summary of new manufacturers' protocols and diagnostic performance: Elena Ivanova (FIND, Switzerland).

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Integration of HCV testing and treatment within harm reduction programming: experiences from Georgia, Kenya, Viet Nam and Myanmar: Ernst Wisse (Médecins du Monde, France).

HCV simplified service delivery on implementation of decentralized and integrated care and task-shifting in Malaysia: operational/implementation issues in national scale-up, Muhammad Radzi Abu Hassan (Ministry of Health, Malaysia).

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Point-of-care HCV RNA viral load: technical specifications and access issues, Emi Elizabeth Okamoto (Clinton Health Access Initiative, USA).

POC HCV RNA viral load: Myanmar: Bridget Louise Draper (Burnet Institute, Australia), Jason Grebely (Kirby Institute/UNSW, Australia).

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ABBREVIATIONS

ALT	alanine aminotransferase
ART	antiretroviral therapy
AST	aspartate aminotransferase
CDC	United States Centers for Disease Control and Prevention
CI	confidence interval
DAA	direct-acting antiviral (drug)
DALY	disability-adjusted life year
DBS	dried blood spot (specimen)
EDTA	ethylenediamine tetraacetic acid
EIA	enzyme immunoassay
EID	early infant diagnosis
ELISA	enzyme-linked immunosorbent assay
EQA	external quality assessment
EQAS	external quality assessment scheme
FDA	United States Food and Drug Administration
FIB-4	fibrosis-4 score
GDP	gross domestic product
GHSS	Global Health Sector Strategy
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HCVcAg	hepatitis C virus core antigen
HCVST	HCV self-testing
HIC	high-income country
HIV	human immunodeficiency virus
HR	hazard ratio
ICER	incremental cost–effectiveness ratio
IFN	interferon
IQC	internal quality control
IQR	interquartile range
IVD	in vitro diagnostic (medical device)
LMICs	low- and middle-income countries
LoD	limit of detection
LY	life year
M&E	monitoring and evaluation

MPP	Medicines Patent Pool
MTCT	mother-to-child transmission
NAT	nucleic acid testing
NGO	nongovernmental organization
NIT	non-invasive test
NPV	negative predictive value
NSP	needle and syringe programme
OR	odds ratio
OAMT	opioid agonist maintenance therapy
PCR	polymerase chain reaction
PEG-IFN	pegylated interferon
PICO	population, intervention, comparison, outcomes
PMTCT	prevention of mother-to-child transmission
POC	point-of-care
PPV	positive predictive value
PQ	(WHO) prequalification
PSC	plasma separation card
QALY	quality-adjusted life year
RBV	ribavirin
RCT	randomized controlled trial
RDT	rapid diagnostic test
RNA	ribonucleic acid
RR	relative risk
SOP	standard operating procedure
SVR	sustained virological response
ULN	upper limit of normal
UPS	uninterruptable power supply
WHO	World Health Organization
WHO GHP	WHO Global Hepatitis Programme

GLOSSARY

Markers for HCV infection

Anti-HCV antibody	Antibody to hepatitis C virus (HCV), which can be detected in the blood usually within two or three months of HCV infection or exposure. The terms HCV antibody and anti-HCV antibody are equivalent, but in these guidelines HCV antibody is used throughout.
HCV RNA	HCV viral genomes that can be detected and quantified in serum by nucleic acid testing (NAT).
HCV core antigen (HCVcAg)	Nucleocapsid peptide 22 [p22] of HCV, which is released into plasma during viral assembly and can be detected from early on and throughout the course of infection.

Natural history of viral hepatitis

Chronic HCV infection	The presence of persistent HCV RNA or HCVcAg in serum in association with positive serology for HCV antibody.
Viraemic infection	Hepatitis C virus infection associated with presence of virus in the blood (as measured by HCV RNA) and often referred to as active, ongoing or current infection.
Cirrhosis	An advanced stage of liver disease characterized by extensive hepatic fibrosis, nodularity of the liver, alteration of liver architecture and disrupted hepatic circulation.
Decompensated cirrhosis	A stage at which clinical (or laboratory) signs of cirrhosis are present. Clinical features include portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy or liver insufficiency (jaundice). Other clinical features of advanced liver disease/cirrhosis may include hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema and oedema. Laboratory features usually present in those with cirrhosis and portal hypertension include a low serum albumin, low platelet count and a prolonged prothrombin time.

Measures of treatment response

HCV sustained virological response (SVR)	Undetectable HCV RNA in the blood at a defined time point after the end of treatment, usually at 12 or 24 weeks (SVR12 or 24).
HCV non-response	Detectable HCV RNA in the blood throughout treatment.
HCV relapse	Undetectable HCV RNA during treatment and/or at end of treatment, but subsequent detectable HCV RNA following treatment cessation.
HCV viral breakthrough	Undetectable HCV RNA during treatment followed by detectable HCV RNA while on continued treatment.

Diagnostic testing for hepatitis C

Serological assays	Assays that detect the presence of either antigens or antibodies, typically in serum or plasma but also in capillary/venous whole blood and oral fluid. These include rapid diagnostic tests (RDTs), laboratory-based immunoassays, for example, enzyme immunoassays (EIAs), chemiluminescence immunoassays (CLIAs), and electro-chemiluminescence immunoassays (ECLs).
Rapid diagnostic test (RDT)	Immunoassays that detect antibodies or antigens or nucleic acid and can give a result in less than one hour. Most RDTs can be performed with capillary whole blood collected by finger-stick sampling.
Enzyme immunoassay (EIA)	Laboratory-based serological immunoassays that detect antibodies, antigens or a combination of both. Requires plasma or serum collected by venepuncture as venous whole blood.
Nucleic acid testing (NAT)	A molecular technology, for example, polymerase chain reaction (PCR) or nucleic acid sequence-based amplification (NASBA) or transcription-mediated amplification (TMA), that can detect very small quantities of viral nucleic acid (RNA, DNA or total nucleic acid (TNA)), qualitatively or quantitatively.
Point-of-care testing	Point-of-care testing is conducted at the site at which clinical care is being provided, with the results being returned to the person being tested or care giver on the same day as sample collection and test to enable clinical decisions to be made in a timely manner.
Reflex viral load testing	A linked HCV RNA (or HCVAg) test that is triggered among all people who have an initial positive HCV antibody screening test. Reflex HCV RNA testing may be implemented in two ways: either laboratory-based reflex testing or clinic-based reflex testing.

- Laboratory-based HCV reflex testing refers to a testing algorithm in which patients have only a single clinical encounter and one blood draw or specimen for an initial laboratory-based HCV antibody test (in some cases it may be divided in two tubes), which is then sent to the lab. If the sample for HCV antibody testing in the lab is positive, then the same existing or a duplicate specimen is automatically used for a prompt "reflex" laboratory-based HCV RNA NAT or HCVAg) test. The result returned to the patient/doctor is, therefore, for both the HCV antibody result and, if positive, the HCV RNA result. No further visit or specimen collection is required.
- Clinic-based reflex testing refers to a testing strategy where there is only a single clinical encounter/visit for an initial rapid diagnostic HCV antibody test, but with two blood draws. A capillary (fingerstick) whole blood specimen is first taken and tested using a rapid diagnostic HCV antibody test, which, if positive (after usually a 15-minute wait), is then immediately followed by a "reflex" second blood specimen collection (either venous blood sample or fingerstick) for HCV RNA detection of current infection. The second blood sample for HCV RNA testing may either be sent to a laboratory for HCV RNA NAT (or HCVAg) test or tested onsite using a point-of-care HCV RNA NAT assay.

Measures of test performance

Clinical/diagnostic sensitivity of a test	The ability of a test to correctly identify those with the infection or disease (that is, true positives/true positives + false negatives).
Clinical/diagnostic specificity of a test	The ability of a test to correctly identify those without the infection or disease (that is, true negatives/true negatives + false positives). Sensitivity and specificity are usually expressed as point estimates accompanied by confidence intervals.
Positive predictive value (PPV)	The probability that when a person's test result is positive, they truly have the infection/disease.
Negative predictive value (NPV)	The probability that when a person's test result is negative, they truly do not have the infection/disease. Predictive values are influenced by the prevalence of the disease in the population.
Analytical sensitivity/limit of detection (LoD)	The lowest concentration of measurement that can be consistently detected in 95% of specimens tested under routine laboratory conditions. It defines the analytical sensitivity, in contrast to the clinical or diagnostic sensitivity.

Populations terminology

Age groups

The following definitions are used in these guidelines for the purpose of implementing treatment recommendations for specific age groups in children aged 3 years and above. It is acknowledged that countries may have other definitions under national laws:

- An adult is a person older than 19 years of age (which includes young people 20–24 years old).
- An adolescent is a person 12–19 years of age inclusive.
- An older child is a person 6–11 years of age.
- A younger child is a person 3–5 years of age.

Key populations

Groups of people who, due to specific high-risk behaviours, are at increased risk for human immunodeficiency virus (HIV) blood-borne infections irrespective of the epidemic type or local context. This term may also apply to hepatitis B virus (HBV) and/or HCV infection. Key populations often have legal and social issues related to their behaviours that increase their vulnerability to HIV, HBV and HCV infection. These guidelines refer to the following groups as key populations: men who have sex with men, people who inject drugs, people in prisons and other closed settings, sex workers and transgender people.

Vulnerable populations

Groups of people who are particularly vulnerable to HBV/HCV infection in certain situations or contexts. These guidelines refer to the following groups as vulnerable populations: migrant and mobile workers; refugee and displaced populations; and indigenous populations. They may also face social and legal barriers to access to viral hepatitis prevention and treatment.

Men who have sex with men

Refers to all men who engage in sexual and/or romantic relations with other men. The words “men” and “sex” are interpreted differently in diverse cultures and societies and by the individuals involved.

People who inject drugs

Refers to people who inject psychotropic (or psychoactive) substances for non-medical purposes. These drugs include, but are not limited to, opioids, amphetamine-type stimulants, cocaine, hypno-sedatives and hallucinogens. Injection may be through intravenous, intramuscular, subcutaneous or other injectable routes.

Sex workers

Includes female, male and transgender adults (18 years of age and above) who receive money or goods in exchange for sexual services, either regularly or occasionally.

Testing approaches	Community-based testing: includes using outreach (mobile) approaches in general and key populations; home-based testing (or door-to-door outreach); testing in workplaces, places of worship, parks, bars and other venues; in schools and other educational establishments; as well as through campaigns.
Facility-based testing	Includes testing in health care settings such as primary care clinics, inpatient wards and outpatient clinics, including specialist dedicated clinics for HIV, viral hepatitis, sexually transmitted infection (STI) and tuberculosis (TB), in district, provincial or regional hospitals and their laboratories, and in private clinical services.

Service delivery terminology

Decentralization	The process of delegating significant authority and resources to lower levels of the health system (provincial, regional, district, sub-district, primary health care and community).
Differentiated service delivery	An approach that simplifies and adapts viral hepatitis services to better serve the needs of people living with viral hepatitis and to optimize the available resources in health systems.
Integration	The co-location and sharing of services and resources across different disease areas. In the context of hepatitis C virus infection, this may include the provision of testing, prevention, care and treatment services alongside other health services, such as HIV, noncommunicable disease (NCD) screening, TB, STI, antenatal clinic (ANC), contraceptive and other family planning services.
Integrated service delivery	Integrated health services are health services that are managed and delivered in a way that ensures people receive a continuum of health promotion, disease prevention, diagnosis, treatment, disease management, rehabilitation and palliative care services, at the different levels and sites of care within the health system and according to their needs throughout the life course.
Task-sharing	The rational redistribution of tasks from "higher-level" cadres of health care providers to other cadres, such as trained lay providers, including community members.
Lay provider:	Any person who performs functions related to health care delivery and has been trained to deliver services but has received no formal professional or paraprofessional certificate or tertiary education degree.
Linkage to care	A process of actions and activities that support people testing for HBV/HCV to engage with prevention, treatment and care services as appropriate for their hepatitis B and C status.
Person-centred care	Care that is focused on and organized around the health needs and expectations of people and communities rather than on diseases.

EXECUTIVE SUMMARY

Hepatitis C virus (HCV) infection is a major public health problem and cause of chronic liver disease that leads to approximately 399 000 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). In 2016, WHO developed the global health sector strategy on viral hepatitis 2016–2021, with the ambitious goal to eliminate viral hepatitis as a public health threat by 2030. While good progress has been made in several champion countries, there remains a major testing and treatment gap. In 2019, only 21% of the 58 million persons with chronic HCV infection had been diagnosed, and 13%, treated. Achieving HCV elimination will require a radical simplification in care pathways to overcome barriers in access to HCV testing and treatment.

The objective of these guidelines is to provide updated evidence-based recommendations on the priority HCV-related topics from the 2018 WHO *Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C infection* and the 2017 WHO *Guidelines on hepatitis B and C testing*. These priority areas are:

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

These guidelines also update existing chapters without new recommendations, such as the inclusion of new manufacturers' protocols on the use of dried blood spot (DBS) for HCV RNA testing and new data to inform the limit of detection for HCV RNA assays as a test of cure, in addition to their use for diagnosis.

Overall, this guideline update is consistent with the modular approach to updating guidelines for diagnosis and treatment of chronic hepatitis B and C virus infections B adopted since 2020 (that is, periodic updating of specific sections or chapters in response to emerging evidence). In July 2021, the first modular update on hepatitis C self-testing guidelines was launched. This guidelines update represents the second modular update on hepatitis C testing and treatment. In 2023, all updates will be compiled along with existing recommendations into a single consolidated guidelines on prevention, testing, care and treatment of hepatitis B and C, containing all relevant guidance.

Five systematic reviews and meta-analyses were undertaken to address the key research questions, in addition to four values and preferences surveys to assess perspectives of affected communities and health workers, cost–effectiveness analyses and a series of case studies on implementation experience to inform the process of formulating recommendations.

The main areas of new recommendations are:

- **Treatment in adolescents and children:** Expansion of the 2018 "treat all" recommendation for all adults to now include all adolescents and children with chronic HCV infection ages three years or older, with use of the same pangenotypic DAA regimens already recommended in adults (sofosbuvir/daclatasvir, sofosbuvir/velpatasvir, glecaprevir/pibrentasvir).
- **Simplified service delivery:** Expansion of HCV testing and treatment services, ideally at the same site, through decentralization of care to lower-level facilities; integration with existing services, such as in primary care, harm reduction, prisons and HIV services; and promotion of task sharing through delivery of HCV testing, care and treatment by trained but non-specialist doctors and nurses.
- **HCV RNA testing:** The use of PoC HCV RNA assays is now recommended as an additional approach to diagnose viraemic infection, especially among marginalized populations, such as persons who inject drugs, and hard-to-reach communities with constrained access to health care and that have high rates of loss to follow-up. Reflex HCV RNA testing in those with a positive HCV antibody is recommended as an additional 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 lab or clinic-based reflex testing in a health facility through immediate specimen collection for HCV RNA testing following a positive rapid HCV antibody test result, avoiding the need for a second visit and further blood sample.

These guidelines are addressed primarily to national hepatitis programme managers and other policy-makers in ministries of health, particularly in LMICs, who are responsible for the development of national hepatitis testing and treatment plans, policy and guidelines. Implementation of the recommendations in these guidelines should be informed by local context, including HCV epidemiology and prevalence of other comorbidities, availability of resources, the organization and capacity of the health system and anticipated cost–effectiveness.

SUMMARY OF RECOMMENDATIONS

The following table presents the recommendations, including the strength of the recommendation and certainty of evidence.

Recommendation	Existing, updated or new recommendation
DAA treatment in adults, adolescents and children	
Whom to treat? 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*	Existing
Adolescents (12–17 years)[1] *strong recommendation; moderate/low certainty of evidence*[2]	New
Older children (6–11 years) *strong recommendation; moderate/very low certainty of evidence*[2]	New
Younger children (3–5 years) *conditional recommendation; very low certainty of evidence*	New
[1] For consistency, the age groupings are the same as those used in the trials for regulatory submissions. [2] Range of certainty of evidence is based on evidence for different DAA regimens.	
What DAA regimens to use? We recommend the use of the following pangenotypic DAA regimens is recommended 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 (younger children).*	New
[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.	

Simplified service delivery	
Decentralization:[1] 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. *(strong recommendation; certainty of evidence:[2] moderate (people who inject drugs, prisoners); low (general population, people living with HIV)*	New
Integration:[3] 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), prisons and HIV/ART services. *(strong recommendation; certainty of evidence: moderate (people who inject drugs, prisoners); low (general population, people living with HIV))*	New
Task sharing:[4] 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)*	New

1 Decentralization of services refers to service delivery at peripheral health facilities, community-based venues and locations beyond hospital sites or conventional health care settings, bringing care nearer to patients' homes.

2 The systematic review was based on an analysis by population group (people who inject drugs, prisoners, general population and people living with HIV) rather than setting or services (harm reduction sites, prisons, primary care or HIV/ART clinics), although these were highly related to population group.

3 Integrated service delivery refers to delivery of different health services in a way that ensures people receive a continuum of health promotion, disease prevention, diagnosis and treatment.

4 Task sharing refers to the rational redistribution of tasks from "higher-level" cadres of health care providers to other cadres, such as trained lay providers, including community members.

HCV RNA testing – Detection of viraemic HCV infection	
Laboratory-based HCV NAT testing: Directly following a positive HCV antibody serological test result, the use of quantitative or qualitative nucleic acid testing (NAT) for detection of HCV ribonucleic acid (RNA) is recommended as the preferred strategy to diagnose viraemic infection. *(strong recommendation, moderate/low certainty of evidence)*	Existing
HCV core antigen assay: An assay to detect HCV core (p22) antigen, which has comparable clinical sensitivity to laboratory-based HCV RNA NAT assays, can be an alternative approach to diagnose HCV viraemic infection. *(conditional recommendation, moderate certainty of evidence)*	Existing
Point-of-care (POC) HCV RNA assays: The use of HCV point-of-care (POC) viral load NAT assay can be an alternative approach to laboratory-based HCV RNA NAT assays to diagnose HCV viraemic infection. *(conditional recommendation, low/moderate certainty of evidence)*	New
HCV RNA testing – Assessment of treatment response	
Laboratory-based HCV RNA NAT assays: Nucleic acid testing (NAT) for qualitative or quantitative detection of HCV RNA should be used as test to document cure at 12 or 24 weeks (that is, sustained virological response (SVR12 or SVR24)) after completion of antiviral treatment. *(conditional recommendation, moderate/low certainty of evidence)*	Existing
Point-of-case HCV RNA assays: 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, low/moderate quality of evidence)*	New
Reflex HCV viral load testing[1]	
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 quality of evidence)*	New

[1] Reflex testing is a linked HCV RNA (or HCVAg) test that is triggered among all people who have an initial positive HCV antibody screening test result. Reflex HCV RNA testing may be implemented in two ways: either laboratory-based reflex testing or clinic-based reflex testing.

Use of dried blood spot (DBS) specimens for serological and virological testing

Existing recommendations from 2017 WHO *Guidelines on hepatitis B and C testing (4)*, now updated with manufacturers' protocols

Topic	Existing recommendations
Serological testing	The use of DBS specimens for HBsAg and HCV antibody serology testing may be considered in settings where: • there are no facilities or expertise to take venous whole blood specimens; or • RDTs are not available or their use is not feasible; or • there are persons with poor venous access (for example, in drug treatment programmes, prisons). *(conditional recommendation, moderate (HBV)/low (HCV) certainty of evidence)*
Detection of viraemia (nucleic acid testing)	The use of DBS specimens to test for HBV DNA and HCV RNA for diagnosis of HBV and HCV viraemia, respectively, may be considered in settings where: • there is a lack of access to sites or nearby laboratory facilities for NAT, or provision for timely delivery of specimens to a laboratory; or • there are persons with poor venous access (for example, in drug treatment programmes, prisons). *(conditional recommendation, low (HBV)/moderate (HCV) certainty of evidence)*

Manufacturers' protocol: Validation of DBS with manufacturers' assays. The use of DBS specimens has now been validated by assay manufacturers with their commercial assays, and under different storage and transport conditions. Manufacturers' protocols are now available that describe procedures for DBS and plasma separation card (PSC) specimen collection, processing, transportation and analysis. These protocols describe procedures for DBS testing using Abbott RealTime HCV assay (Abbott Molecular Inc, USA), Cobas® HCV for use on the Cobas® 6800/8800 Systems, Cobas® HCV for use on the Cobas® 4800 Systems (Roche Molecular Systems, USA) and Aptima® HCV Quant Dx Assay (Hologic, USA).

Updated WHO *Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations* (WHO, 2022) *(7)*

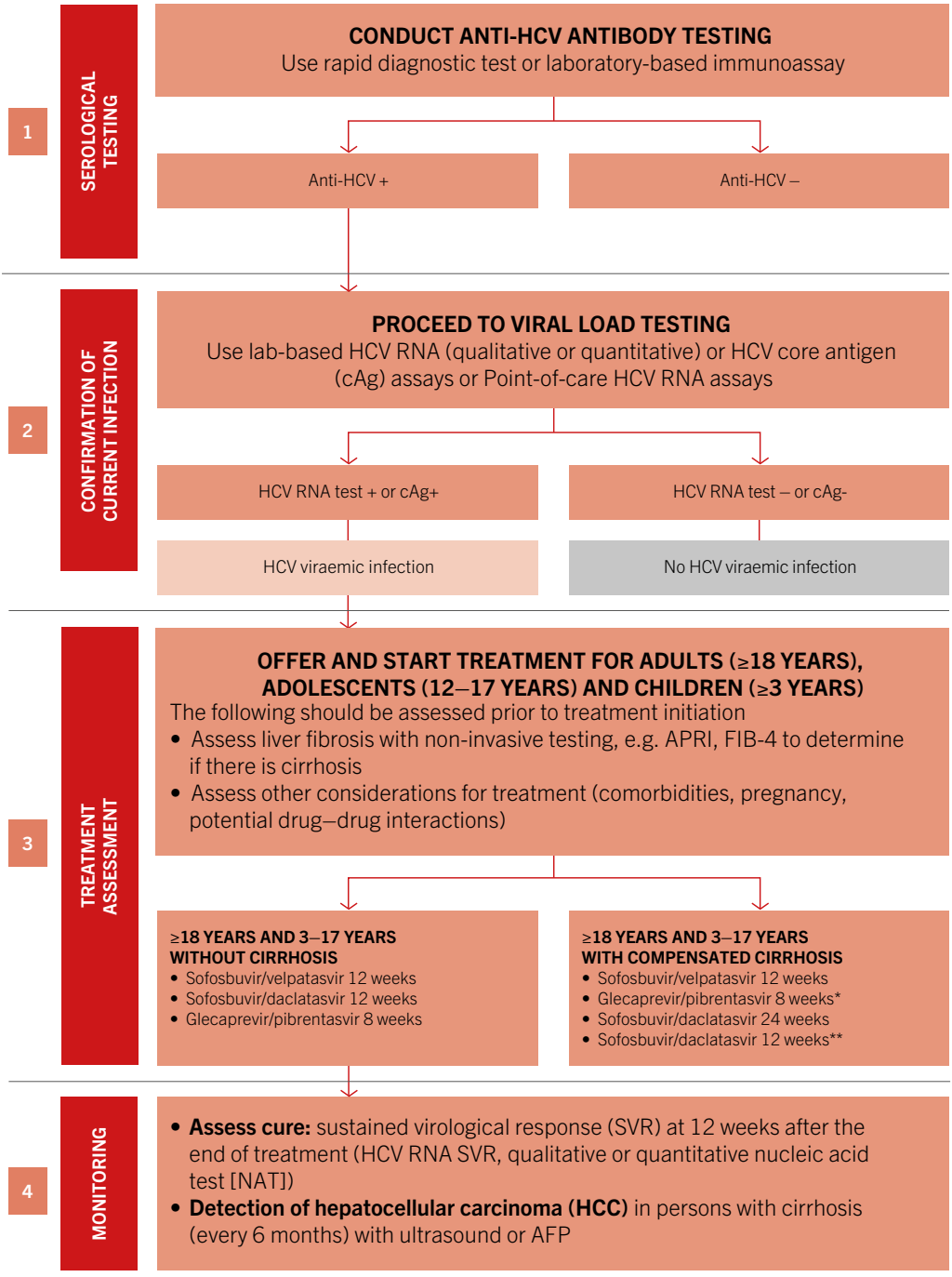
An updated version of the *Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations* (WHO, 2022) *(7)* will be published in July 2022. This guidance outlines a public health response to HIV, viral hepatitis and sexually transmitted infections (STIs) for five key populations, notably men who have sex with men, sex workers, people in prisons and other closed settings, people who inject drugs and trans and gender diverse.

The guidelines include a new recommendation on peer navigators to support people from key populations to start HIV, viral hepatitis or STI treatment and to remain in care, as well as a new recommendation on offering online delivery of HIV, viral hepatitis and STI services to key populations as an additional option, while ensuring that data security and confidentiality are protected. It includes new good practice statements on chemsex and behavioural interventions.

There are two recommendations directly relevant to HCV testing and treatment:

- People at ongoing risk and a history of treatment-induced or spontaneous clearance of HCV infection may be offered 3–6 monthly testing for presence of HCV viraemia (conditional recommendation, very low certainty of evidence).
- Pangenotypic DAA-HCV treatment should be offered without delay to people with recently acquired HCV infection and ongoing risk.

FIGURE 1 Summary algorithm on HCV testing and treatment



* Persons who failed prior therapy with interferon, ribavirin, and/or sofosbuvir with HCV genotype 1, 2, 4–6 with cirrhosis should be treated for 12 weeks, and with HCV genotype 3 with or without cirrhosis should be treated for 16 weeks.

CHAPTER 1. INTRODUCTION

1.1 Objectives and scope of updated HCV guidelines

The objective of these updated guidelines is to provide updated evidence-based recommendations on key HCV-related topics identified in both the 2018 WHO *Guidelines for the care and treatment of persons diagnosed with chronic HCV infection (1)* and the 2017 WHO *Guidelines on hepatitis B and C testing (4)*. The three priority areas are:

- use of direct-acting antiviral (DAA) treatment of adolescents and children ages ≥3 years
- simplified service delivery (decentralization, integration and task sharing)
- HCV diagnostics – use of PoC HCV RNA viral load and reflex HCV RNA viral load testing.

These guidelines also include updates to existing chapters without any new recommendations, such as inclusion of new manufacturers' protocols on use of dried blood spots (DBS) for serology and HCV RNA viral load testing and new data to inform limit of detection for HCV RNA viral load assays as a test of cure.

Overall, this guideline update is consistent with the modular approach to updates adopted since 2020 in response to emerging evidence on hepatitis B and C virus infections. The first modular update, on hepatitis C self-testing, was launched in July 2021 *(5)*. This guidelines update constitutes the second modular update on hepatitis C testing and treatment. A modular update on hepatitis B testing and treatment is planned for 2022 based on existing hepatitis B treatment *(6)* and testing guidelines *(4)*. In 2023, all updates will be compiled along with existing recommendations into a single consolidated guidelines on prevention, testing, care and treatment of hepatitis B and C, containing all relevant guidance.

1.2 Related guidelines

These guidelines are intended to complement existing guidance on the primary prevention of HCV and other bloodborne viruses by improving blood and injection safety, and health care for people who inject drugs and other vulnerable groups, including those living with HIV.

Additional guidance relevant to the prevention, care and treatment of those infected with HCV can be found in the following documents:

- WHO *Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection (2018) (1)*
- WHO *Guidelines on hepatitis B and C testing (2017) (4)*
- *Recommendations and guidance on hepatitis C virus self-testing (2021) (5)*

- *Guidelines for the prevention, care and treatment of persons with chronic hepatitis B virus infection (2015) (6)*
- *Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations* (2022 update) *(7)*
- *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (2021) (2).*

1.3 Intended audience

These guidelines are primarily addressed to national hepatitis programme managers and other policy-makers in ministries of health, particularly in LMICs, who are responsible for the development of national hepatitis testing and treatment plans, policy and guidelines. These guidelines will also be useful for laboratory managers in ministries of health, reference laboratories and key hospital laboratories who are responsible for validation of assays, development of national testing algorithms, and national procurement of assays, quality control (QC) and quality assurance (QA). Finally, the guidelines will serve as a reference for health care providers who offer and implement hepatitis testing, care and treatment for persons with hepatitis C virus infection, including those working in community-based programmes.

1.4 Guiding principles

The following principles have informed the development of these guidelines and should guide the implementation of the recommendations.

1.4.1 The public health approach

The guidelines are based on and are intended to support a public health approach to scaling up the use of antiviral treatment for HCV infection along the continuum of hepatitis prevention, diagnosis, linkage to care and treatment.

In recognition of the importance of streamlined, standardized approaches to scaling up HCV services in settings with limited resources, the public health approach emphasizes strategies such as task sharing, decentralization, integration of HCV testing and treatment services with other public health programmes and patient, and community empowerment. High-income countries with more resources and fewer HCV cases may favour a more individualized approach to care, although the overarching framework of the public health approach provides the setting for scale-up of testing and treatment, within which this more personalized service delivery can occur.

1.4.2 People-centred care

People-centred health services are an approach to care that consciously adopts the perspectives of individuals, families and communities and sees them as participants and beneficiaries of trusted health systems that respond to their needs and preferences in humane and holistic ways. This approach acknowledges the experiences and perspectives of health care providers that may enable or prevent the delivery of people-centred care of high quality.

The public health approach recognizes the importance of streamlined, standardized approaches to scaling up HCV services in settings with limited resources.

1.4.3 Essential strategies for an enabling environment for key populations

Implementation of the guidelines needs to be accompanied by efforts to promote and protect the human rights of people who need hepatitis services, including ensuring informed consent, preventing stigma and discrimination in the provision of services and promoting gender equity.

Several populations are subject to structural barriers to health care, including stigma, discrimination, marginalization, criminalization and violence. This is especially important for women, young girls and adolescents and key populations, who are subject to these barriers across the HIV and hepatitis care cascade. Although primarily intended for developing programmatic guidance to help implement all WHO recommendations, the basic principles underlying these recommendations align with the concepts of people-centred care, the public health approach and a rights-based approach.

The updated WHO *Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations*, 2022 update) *(7)* describe essential strategies to build an enabling environment. They include developing supportive legislation and policy, including working towards decriminalizing drug use and possession, sexual orientation and gender identity addressing stigma and discrimination, empowering communities, and addressing violence against key populations. WHO also supports a strong emphasis on workforce training against stigma and discrimination and strategies to support those that are subject to violence, to ensure that all populations benefit from access to better and safer health care services.

1.4.4 Adaptation of implementation to local context

Implementation of the recommendations in these guidelines should be informed by local context, including HCV epidemiology and the prevalence of other comorbidities, the availability of resources, the organization and capacity of the health system and anticipated cost–effectiveness.

CHAPTER 2. BACKGROUND – EPIDEMIOLOGY AND NATURAL HISTORY

2.1 Epidemiology of HCV infection and the challenge of HCV elimination

HCV infection is a major public health problem and cause of liver disease that leads to approximately 399 000 deaths annually, mainly from cirrhosis or hepatocellular carcinoma (HCC) *(9)*. In 2019, WHO estimated that 58 million persons were chronically infected, with a disproportionately high burden in low- and middle-income countries (LMICs). WHO estimated that, in 2019, 1.5 million new HCV infections occurred, mostly through injecting drug use; sexual transmission, especially among men who have sex with men; and unsafe health care practices *(9)*. Worldwide, HCV infection may be caused by any of six major HCV genotypes. Their distribution varies by geographic region *(9)*.

In May 2016, the Sixty-ninth World Health Assembly endorsed the global health sector strategy (GHSS) for 2016–2021 on viral hepatitis (HBV and HCV infection), with the ambitious goal to eliminate viral hepatitis as a public health threat by 2030 *(10)*. A new integrated HIV, hepatitis and sexually transmitted infections global strategy GHSS *(2022-2030)* was endorsed at the Seventy-fifth World Health Assembly in May 2022.[1] Elimination is defined as a 90% reduction in new chronic infections and a 65% reduction in mortality compared with a 2015 baseline. Reaching these targets will require scale-up of currently available prevention interventions as well as testing and treatment to achieve diagnosis of 90% of those infected and treatment of 80% of those diagnosed as infected. Several champion countries have made good progress in the scale-up of treatment access and of highly effective preventative approaches such as assuring blood and injection safety. However, there remain major gaps in the cascade of testing and treatment of those living with hepatitis C. In 2019, of the 58 million persons with HCV infection, 21% had been diagnosed, and 13% had been treated *(9)*.

Major gaps remain in testing and treatment: Only 21% of those infected have been diagnosed, and only 13%, treated.

[1] World Health Organization. "Final Draft Global Health Sector Strategies on Hiv, Viral Hepatitis and Sexually Transmitted Infections 2022-2030 " Last modified 2022. Accessed June 6, 2022. https://cdn.who.int/media/docs/default-source/hq-hiv-hepatitis-and-stis-library/full-draft-who-ghss-hiv-vh-sti_1-may_final.pdf?sfvrsn=35aa9640_3.

2.2 Natural history of HCV infection

2.2.1 Disease progression

HCV infection causes both acute and chronic hepatitis. Incident infection is associated with early symptoms in about approximately 20% of persons. Spontaneous clearance in the absence of treatment occurs within six months of infection in around 25% of infected individuals *(11)*. The remaining 55–85% develop chronic infection, which can lead to progressive fibrosis and cirrhosis. The risk of cirrhosis in those with chronic hepatitis C infection ranges from 15% to 30% after about 20 years of infection with HCV *(12-14)*. Initially, cirrhosis is usually compensated. Decompensated cirrhosis (liver failure) may subsequently occur, leading to morbidity and mortality from outcomes including variceal haemorrhages, ascites, spontaneous bacterial peritonitis or encephalopathy, and renal impairment *(15)*. Annually, approximately 1–3% of persons with cirrhosis progress to HCC *(16)*. The risk of progression to cirrhosis and HCC varies according to both host and virological factors. Age of acquisition, alcohol use, HBV or HIV coinfection and immunosuppression due to any cause increase the risk of developing cirrhosis or HCC *(17, 18)*. In the absence of antiretroviral (ART) treatment, HIV co-infected persons, particularly those with advanced immunodeficiency (CD4 count <200 cells/mm3), progress to cirrhosis, decompensated cirrhosis and HCC significantly faster than do HCV mono-infected persons *(17, 19, 20)*.

2.2.2 Extrahepatic manifestations

HCV infection can also lead to extrahepatic manifestations *(21)*. Among HCV-infected persons, the three most common comorbidities are depression (24%), diabetes mellitus (15%) and chronic renal disease (10%). Less common are immune-related extrahepatic manifestations (for example, mixed cryoglobulinemia, B-cell non-Hodgkin lymphoma and idiopathic thromobocytopaenic purpura (ITP). A proportion of these morbidities is directly attributable to HCV infection and is, therefore, referred to as extrahepatic manifestations. Extrahepatic manifestations are likely to improve with treatment. The prevalence of these extrahepatic manifestations is usually independent of the degree of liver fibrosis *(22, 23)*.

2.3 Routes of transmission

2.3.1 Health care-associated transmission

In countries where infection prevention and control measures are insufficient, HCV infection is associated with unsafe health care injection practices and procedures such as renal dialysis, surgery, dental care and unscreened blood transfusions *(24-26)*. Worldwide, in 2010 an estimated 5% of health care injections were given with unsterilized, reused injection devices *(27)*, and unsafe injections were estimated to lead to 315 000 new HCV infections each year *(28)*. Excessive use of injections to administer medications, coupled with poor injection practices, further increases HCV transmission *(29)*. This persisting driver of transmission needs to be addressed through safer health care, introduction of reuse-prevention injection devices *(30)* and a reduction in unnecessary health care injections.

2.3.2 Transmission among people who inject drugs

Globally, injection drug use may account for 23% of new HCV infections; 8% of current HCV infections are among people who inject drugs *(9)*. People who inject drugs who are infected with HCV are at increased risk of all-cause mortality, reflecting the combined role of injecting drug use, low socioeconomic status, poor access to health care and environmental factors *(31, 32)*.

2.3.3 Other modes of transmission

Other modes of HCV transmission include mother-to-child transmission, which affects 4–8% of children born to women with HCV infection and 10.8–25% of children born to women with HIV/HCV coinfection *(33)*; other percutaneous procedures, such as tattooing and body piercing *(34)*; and needlestick injuries in health care workers *(35, 36)*. Sexual transmission of HCV occurs infrequently in heterosexual couples. It is more frequent in men who have sex with men *(37)*. Transmission among HIV-negative men who have sex with men is increasing.

2.4 Direct-acting antivirals

2.4.1. Summary of the currently available pangenotypic DAA combinations

DAAs are considered pangenotypic when they achieve high treatment efficacy across all six major HCV genotypes. Pangenotypic DAAs simplify the care pathway by removing the need for expensive genotyping and so streamline procurement and supply chains and expand global treatment access.

Sofosbuvir/velpatasvir

Sofosbuvir/velpatasvir is a fixed-dose combination (FDC) of a pangenotypic NS5A inhibitor and sofosbuvir. It was approved both by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2016. In clinical trials it is associated with high efficacy against infections with genotypes 1–6, HIV/HCV coinfection, persons on opioid agonist maintenance therapy (OAMT) and persons with compensated or decompensated cirrhosis *(38-42)*. Sofosbuvir/velpatasvir retains high efficacy with genotype 4 non-A/D subtypes, which are endemic in some regions of sub-Saharan Africa *(43)*.

Glecaprevir/pibrentasvir

Glecaprevir/pibrentasvir is an FDC containing a pangenotypic NS3/4A protease inhibitor with a pangenotypic NS5A inhibitor. The FDA and EMA approved it in 2017. In clinical trials it is associated with high efficacy against infections with genotypes 1–6 and compensated cirrhosis, including in persons with renal insufficiency and end-stage renal disease *(44-50)*. The regimen is contraindicated in persons with decompensated cirrhosis (Child–Pugh Class C) because of high exposure to the protease inhibitor.

Sofosbuvir/daclatasvir

Daclatasvir, an NS5A inhibitor that has been evaluated with sofosbuvir, was approved by the EMA in 2014 and by the FDA in 2015. Clinical trials reported high efficacy of the combination of daclatasvir and sofosbuvir in infections with genotypes 1–4, persons with decompensated liver disease, liver transplant recipients and those with HIV/HCV coinfection *(51-53)*. Other data showed that the combination is also effective in infections with genotypes 5 and 6. Sofosbuvir/daclatasvir and also sofosbuvir/ledipasvir may be less effective against certain HCV genotypes, namely genotype 4 non-A/D subtypes, which are endemic in some regions of sub-Saharan Africa, as well as other genotypes elsewhere (including genotypes 1 and 3), which frequently contain resistance-associated substitutions in the NS5A regions *(54)*.

Sofosbuvir/velpatasvir/voxilaprevir

Sofosbuvir/velpatasvir/voxilaprevir is generally considered for use in the retreatment of HCV-infected persons who previously failed a DAA regimen. In some high-income countries, however, it is also registered for treatment-naive HCV-infected persons. An updated review of retreatment of persons with DAA failure is planned for 2022.

2.4.2 Access to direct-acting antivirals

DAAs for HCV infection were initially sold at a very high price, limiting access. Opportunities to access low-price generic medicines are increasing, however, particularly in LMICs *(55)*.

CHAPTER 3. METHODOLOGY AND PROCESS OF DEVELOPING THE GUIDELINES

3.1 Overview

These current guidelines constitute an update with new recommendations on key HCV-related topics and chapters from both the 2018 WHO *Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection (1)* and the 2017 WHO *Guidelines on hepatitis B and C testing (4)*. These include: use of direct-acting antiretroviral (DAA) treatment in adolescents and children ages ≥3 years, simplified service delivery (decentralization, integration and task sharing), and use of POC HCV RNA viral load assays for diagnosis and as a test of cure, and reflex HCV viral load testing.

These guidelines also include updates to existing chapters without any new recommendations, such as on use of dried blood spot (DBS) for serology and HCV ribonucleic acid (RNA) viral load testing (inclusion of new manufacturers' protocols), and new data to inform limit of detection for HCV RNA viral load assays as a test of cure.

Overall, this guideline update is consistent with the modular approach to updates adopted since 2020 in response to emerging evidence on hepatitis B and C virus infections. The first modular update, on hepatitis C self-testing guidelines, was launched in July 2021 *(5)*. This guidelines update is the second modular update on hepatitis C testing and treatment. A modular update on hepatitis B testing and treatment, based on existing hepatitis B treatment and testing guidelines *(4, 6)*, is planned for 2022. In 2023 all updates will be compiled along with existing recommendations into a single consolidated guidelines on prevention, testing, care and treatment of hepatitis B and C, containing all relevant guidance.

3.2 WHO guideline development process

The WHO Department of HIV, Hepatitis and STI Global Programmes led the development of these updated guidelines on priority areas of HCV testing, care and treatment, following the WHO procedures and reporting standards laid out in the *WHO handbook for guideline development*, second edition, 2014 *(56)*. The recommendations in the guidelines are based on the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to reviewing evidence and formulating recommendations *(57-61)* .

3.3 Roles (Web Annex A)

A WHO Steering Committee was constituted, which included individuals with relevant expertise from different WHO units, who oversaw the guidelines development process. A Guidelines Development Group was constituted to ensure representation from various stakeholder groups, including members of organizations that represent patients' groups, advocacy groups, researchers and clinicians. Group members were also selected to achieve geographical representation and gender balance. There was an initial scoping and planning process to formulate questions most relevant to LMICs and to define outcomes important to patients. The Guidelines Development Group helped formulate the questions on population, intervention, comparison, outcomes (PICO), reviewed the evidence profiles and decision-making tables, composed and agreed upon the wording of the recommendations, and reviewed drafts of the guidelines document. The guidelines methodologist ensured that the GRADE framework was appropriately applied throughout the guideline's development process. This included formulation of the population–intervention–comparison–outcomes (PICO) questions, ensuring the comprehensiveness and quality of the systematic reviews, and preparing evidence profiles and decision-making tables, including certainty of evidence. The methodologist also provided guidance to the Guidelines Development Group in formulating the wording and strength of the recommendations. The External Review Group reviewed the draft guidelines document and provided crucial feedback.

3.4 Evidence that informed the recommendations (Web Annex B)

Systematic reviews, meta-analyses, cost–effectiveness analyses, values and preferences surveys and a series of case studies on implementation experience, to inform feasibility, were undertaken to support the process of formulating recommendations and identifying outcomes important to patients.

3.4.1. Systematic reviews and meta-analyses (Web Annex C)

Five systematic external reviews and meta-analyses of the primary literature were commissioned externally to address the research questions and outcomes important to patients. Outcomes were ranked by the Guidelines Development Group based on their importance to the patient population.

These included:

- the efficacy and safety of direct-acting antivirals in children and adolescents with chronic HCV infection;
- decentralization, integration and task-sharing in hepatitis C virus infection testing and treatment;
- impact of HCV PoC HCV RNA viral load testing on uptake of testing and treatment and turnaround times and diagnostic accuracy of PoC HCV RNA viral load assays;
- determining the threshold/lower limit of detection required for HCV RNA viral load assays for test of cure following treatment with direct-acting antiviral (DAA) based treatment regimens;
- laboratory-based and clinic-based HCV viral load reflex testing following an initial positive HCV antibody test result.

Search strategies and summaries of evidence are reported in Web Annex A. GRADE tables for all reviews are reported in Web Annex C. Evidence-to-decision tables appear in Web Annex C. The glossary provides full definitions for diagnostic and analytical test performance.

3.4.2 Values and preferences and acceptability surveys (Web Annex D)

Simplified service delivery and PoC HCV diagnostics. WHO commissioned three related surveys or in-depth interviews from different partner organizations, which were undertaken among different populations affected by HCV to inform an understanding of the values, preferences and acceptability of different ways of simplifying delivery of care and treatment for chronic HCV infection (that is, decentralization, integration and task sharing of HCV services) and on simplifying HCV diagnostic pathways, including use of PoC HCV RNA viral load diagnostic assays. These included the following:

(i) A multi-country online survey, comprising 42 questions, was conducted by the World Hepatitis Alliance and Coalition Plus in September 2021, disseminated through partner networks and social media. There were 210 respondents from 49 countries.

(ii) A series of peer-driven semi-structured interviews (SSI) or focus group discussions (FGD) conducted by the International Network of People Who Use Drugs (INPUD) from April to June 2021 among four key populations (gay and bisexual men, male and female sex workers, people who inject drugs and transgender people). Some 230 individuals participated from 68 countries.

(iii) A multi-country rapid qualitative assessment using a master protocol across 10 countries, commissioned by FIND in 2020 to understand the values and preferences concerning hepatitis C self-testing (HCVST) as well as perspectives on current hepatitis C testing services among potential service end-users (general population and marginalized populations) and health care workers. Some 460 people from 10 countries participated in individual interviews, and 220, in group interviews.

Treatment of children and adolescents: A further online survey was commissioned and undertaken between August and September 2021 across global, regional and country networks of paediatricians treating HCV-infected children and adolescents. The survey assessed preferences and acceptability regarding which children to prioritize for treatment and which DAA regimens to use. Networks included: PENTA Child Health network, Federation of International Societies of Paediatric Gastroenterology, Hepatology and Nutrition (FISPGHAN) and regional counterparts – the Asian Pan-Pacific Society (APPSPGHAN); the Commonwealth Association of Paediatric Gastroenterology and Nutrition (CAPGAN); the European Society (ESPGHAN); the Latin American Society (LASPGHAN); the North America Society (NASPGHAN); and the Pan Arab Society (PASPGHAN). Some 142 health care workers responded, of whom 94 had treated HCV-infected children or adolescents within the previous three years. Practitioners from all WHO geographic regions were represented; the highest proportions of respondents were from the Western Pacific (43%) and the Americas (19%).

3.4.3 Feasibility – case studies on operational and implementation experience

Case studies were commissioned from programmes in several countries to obtain information on the operational experience and feasibility of decentralization, integration, and task-sharing; use of PoC HCV RNA viral load assays in outreach clinic services for people who inject drugs and the general population; and use of laboratory-based HCV reflex viral load testing. The case studies focused on description of the model, key outcomes, challenges and operational lessons learned.

3.4.4 Cost–effectiveness analyses

All commissioned systematic reviews captured relevant literature that had evaluated the cost–effectiveness and population health outcomes of different levels of decentralization and task-sharing, use of PoC HCV RNA viral load and use of reflex HCV RNA viral load testing. Also, the Clinton Health Access Initiative (CHAI) was commissioned to undertake a market size analysis of paediatric DAA dosage forms *(62)* and an assessment of DAA generic supplier status to inform a feasibility assessment of different DAA treatment options for younger children.

3.5 Grading of certainty of evidence and strength of recommendations (Web Annex B)

The certainty of the evidence was assessed and either rated down or rated up based on criteria specified in GRADE methods, modified for diagnostic tests and test strategies *(63, 64)*. Summaries of the certainty of evidence to address each outcome were entered in the GRADE profiler software GRADE pro 3.6. The certainty of evidence was categorized as high, moderate, low or very low (Box 3.1 and Table 3.1).

Specific issues with rating the certainty of evidence for studies of diagnostic accuracy

For evaluation of POC RNA viral load diagnostics, the Guidelines Development Group considered

BOX 3.1 Standard approach to rating the certainty of evidence and strength of recommendations using the GRADE system

The GRADE system separates the rating of the certainty of evidence from the rating of the strength of the recommendation.

The **certainty of evidence** is defined as the confidence that the reported estimates of effect are adequate to support a specific recommendation. The GRADE system classifies the certainty of evidence as high, moderate, low or very low, indicating the level of confidence in the estimates and findings (Table 3.1). For studies of interventions, randomized controlled trials (RCTs) are initially rated as high-certainty evidence but may be downgraded for several reasons, including the risk of bias, inconsistency of results across studies, indirectness of evidence, imprecision and publication bias. Observational studies of interventions are initially rated as low-certainty evidence but may be upgraded if the magnitude of the treatment effect is very large, if multiple studies show the same effect, if evidence indicates a dose–response relationship or if all plausible biases would underestimate the effect. The higher the certainty of evidence, the more likely a strong recommendation can be made.

The **strength of a recommendation** reflects the extent to which the Guidelines Development Group was confident that the desirable effects of following a recommendation outweigh the potential undesirable effects. The strength is influenced by the following factors: the certainty of the evidence, the balance of benefits and harms, values and preferences, resource use and the feasibility of carrying out the intervention (Table 3.2).

The GRADE system classifies the strength of a recommendation in two ways: "strong" and "conditional" *(65)*.

A strong recommendation is one for which the Guidelines Development Group was confident that the desirable effects of adhering to the recommendation outweigh the undesirable effects.

A conditional recommendation is one for which the Guidelines Development Group concluded that the desirable effects of adhering to the recommendation probably outweigh the undesirable effects but the Guidelines Development Group is not confident about these trade-offs. The implications of a conditional recommendation are that, although most people or settings would adopt the recommendation, some would not or would do so only under certain conditions. The reasons for making a conditional recommendation include the absence of high-certainty evidence, imprecision in outcome estimates, uncertainty regarding how individuals value the outcomes, small benefits relative to harms, and benefits that may not be worth the costs (including the costs of implementing the recommendation).

outcomes important to patients, diagnostic accuracy (sensitivity, specificity, positive and negative predictive values) and in some cases analytical sensitivity (limit of detection). Although observational studies of interventions start as low certainty in GRADE, cross-sectional and cohort studies of diagnostic accuracy can provide reliable evidence on diagnostic accuracy *(63)* and, therefore, were initially categorized as high certainty. Evidence was then rated down based on the presence of (i) risk of bias (using a tool designed for assessment of diagnostic accuracy studies, the QUADAS-2 tool) *(66)*; (ii) inconsistency (indicated by heterogeneity); (iii) indirectness (for example, addressing a different population than the one under consideration); or (iv) imprecision. For diagnostic accuracy studies, evaluating inconsistency is a challenge because methods to measure statistical heterogeneity that account for threshold effects are lacking, and statistical heterogeneity is usually high even when diagnostic accuracy estimates are fairly close. Therefore, inconsistency for diagnostic accuracy outcomes was based on whether variability in estimates exceeded pre-defined thresholds (for example, the variability in sensitivity estimates exceeded 0.10). Although diagnostic accuracy is an intermediate outcome, we did not downgrade for indirectness because diagnostic accuracy was a pre-defined outcome of interest.

TABLE 3.1 GRADE categories of the certainty of evidence

Certainty of evidence	Rationale
High	We are very confident that the true effect lies close to the estimate of effect.
Moderate	We are moderately confident of the estimate of effect. The true effect is likely to be close to the estimate of effect, but it could be substantially different.
Low	Our confidence in the estimate of effect is limited. The true effect may be substantially different from the estimate of effect.
Very low	We have very little confidence in the estimate of effect. Any estimate of effect is very uncertain.
Simeprevir	Pibrentasvir

TABLE 3.2 Key domains considered in determining the strength of recommendations

Domain	Rationale
Benefits and harm	When a new recommendation is developed, desirable effects (benefits) need to be weighed against undesirable effects (risks or harm), considering any previous recommendation or an alternative. The larger the gap or gradient in favour of the benefits over the risks, the more likely that a strong recommendation will be made.
Certainty of evidence	High certainty of evidence is likely to lead to a strong recommendation.
Values and preferences (of providers and stakeholders)	If decisions to use an intervention are unlikely to be affected by differences in how providers, end-users and other stakeholders value various outcomes, it is more likely that a strong recommendation will be made. If there is a high degree of variability or uncertainty with regard to how providers and stakeholders value various outcomes, that could impact the decision; a conditional recommendation is more likely.
Acceptability (of providers and stakeholders)	If the recommendation is likely to be widely accepted or highly valued, it is likely that a strong recommendation will be made. If there is a great deal of variability or strong reasons that the recommended course of action is unlikely to be accepted, it is more likely that a conditional recommendation will be made.
Cost/financial implications	Lower costs (monetary, infrastructure, equipment or human resources) or greater cost–effectiveness contribute to a strong recommendation.
Feasibility	If an intervention is achievable in a setting where the greatest impact is expected, a strong recommendation is appropriate.
Equity and human rights	If the recommendation is likely to increase access to an intervention for those most in need, a strong recommendation is likely.
Acceptability	The greater the acceptability to all or most stakeholders, the greater the likelihood of a strong recommendation

3.6 Formulation of recommendations

At the Guidelines Development Group meeting, the results of the systematic reviews, meta-analyses and complementary information were presented, and the evidence profiles and decision-making tables were reviewed to ensure that participants understood and agreed on the scoring criteria (see Web Annex C).

The GRADE method was used to rate the quality of the evidence and determine the strength of the recommendations. The strength of the recommendations was rated as either strong (the panel was confident that the desirable effects of the intervention outweighed the undesirable effects) or conditional (the panel determined that the desirable effects of the intervention probably outweighed the undesirable effects). The certainty of evidence supporting each recommendation was graded as high, moderate, low or very low. Recommendations were then formulated by members of the Guidelines Development Group through discussions based on overall certainty of the evidence, in addition to other considerations, including the balance of benefits and harms,

values, preferences and acceptability, resource implications and the feasibility of carrying out the intervention. The chairs and methodologist worked to reach consensus during the meeting. After discussion of all comments and questions from members of the Group, the Chair, to document consensus, asked Group members whether they agreed with the recommendations. Voting was not required, but the group had agreed *a priori* that two thirds of the votes would be required for a decision. All Group members agreed with all the recommendations. For each recommendation, the Group evaluated also the implementation needs and identified areas and topics requiring further research. Prior to finalization, Guidelines Development Group and an external review group reviewed and further revised the draft guidelines.

3.7 Declarations of interest and management of conflicts of interest

In accordance with WHO policy, all external contributors to the guidelines, including members of the Guidelines Development Group and the External Review Group, completed a WHO declaration of interest form (including participation in consulting and advisory panels, research support and financial investment). Prior to the guideline meeting, a brief biography of each member of the Guidelines Development Group was posted on the website. The WHO Steering Committee reviewed and assessed the declarations submitted by each member and agreed on an approach to assess potential conflicts of interest. At the meeting, declarations of interest were reported according to WHO standard requirements. Individuals from organizations that had received significant funding from private (primarily pharmaceutical) companies and individual researchers or clinicians who had received honoraria above US$ 5000 from pharmaceutical companies were considered to have a conflict of interest if it was related to the guidelines topic and recommendations, and their participation in the Guidelines Development Group was classified as restricted (Web Annex E). The participation of only one group member, Jason Grebely, was restricted for the topic of PoC HCV RNA viral load assays. This group member contributed his technical expertise in reviewing the evidence summaries but was excluded from participation in voting and formulation of the recommendation (Web Annex A).

The declarations of interest forms from members of the External Review Group were reviewed in accordance with the WHO guidelines development policy. For the peer review group, the WHO Secretariat was satisfied that no case necessitated exclusion from the review process. Any conflicts of interest identified were considered when interpreting comments from External Review Group members during the external review process. The external reviewers could not and did not make changes in the recommendations.

3.8 Dissemination and updating of the guidelines

The guidelines update will be disseminated electronically on the WHO HHS departmental website and to WHO regional offices, WHO country offices and ministries of health through webinar series, made available as a print publication on demand and as policy briefs. Dissemination will be further supported by publication of the systematic reviews and evidence in peer-reviewed journals.

The successful implementation of the recommendations in these guidelines will depend on a well-planned and appropriate process of adaptation and integration into relevant regional and national strategies. Implementation of these guidelines can be measured by the number of countries that incorporate them into their national treatment programmes and updated data on uptake of HCV viral load testing and treatment, which is part of the cascade of care monitoring and evaluation framework. WHO monitors numbers of HCV infected adults who have been treated, and now also HCV infected adolescents and children.

These guidelines will be updated in full or in part based on regular scoping exercises of available evidence and experience from country implementation that will guide and trigger the need for new guidance. As the evidence base or user needs change, consideration will be given to producing technical updates on specific subjects.

TREATMENT OF ADULTS, ADOLESCENTS AND CHILDREN ≥ 3 YEARS

CHAPTER 4. TREATMENT FOR ADULTS, ADOLESCENTS AND CHILDREN (≥3 YEARS)

4.1 New recommendations: treatment of adolescents (12–17 years), older children (6–11 years) and younger children (3–5 years); and existing 2018 recommendations for adults *(1)*

Whom to treat?

New recommendations (for adolescents and children) and existing recommendations for adults *(1)*

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

Adults (≥18 years)[1]: *strong recommendations; moderate certainty of evidence*

Adolescents (12–17 years)[2]: *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] Existing 2018 recommendation from Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C infection *(1)*. Pangenotypic is defined as SVR rate of >85% across all six major HCV genotypes.

[2] 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) and existing recommendations for adults *(1)*

We recommend the use of the following pangenotypic DAA regimens is recommended 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 (younger 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.

TABLE 4.1. Duration of treatment

Age groups	Pangenotypic DAA regimens			Non-pangenotypic DAA regimen (in settings with minimal GT3 infection)[2]
	Sofosbuvir/ daclatasvir[1]	Sofosbuvir/ velpatasvir[2]	Glecaprevir/ pibrentasvir	Sofosbuvir/ ledipasvir2
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 4.2. Dosing by weight bands

Pangenotypic DAA regimens			Non-pangenotypic DAA regimens (in settings with minimal GT3 infection)[1]
Sofosbuvir/ daclatasvir[2]	**Sofosbuvir/ velpatasvir**	**Glecaprevir/ pibrentasvir[3]**	Sofosbuvir/ ledipasvir
>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)	≥35kg 90/400 mg od (FDC tablet)
14–25 kg 200 mg/30 mg[2] (as single tablets, sofosbuvir 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– 35kg 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)

[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) a sustained virological response (SVR) with sofosbuvir (400 mg) and ledipasvir (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. Realistically, these findings do not support the use of sofosbuvir–ledipasvir as the initial therapy for HCV infection 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 and oral pellets or granules 50/20 mg, depending on locally approved product information

4.2 Background

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. This result has been due to high efficacy and minimal side effects with short-course treatment compared with the previous era of interferon-based regimens. Until recently, there had been less attention to addressing HCV in children and adolescents, and no DAA regimens were approved for use in children *(67, 68)*.

In 2018 there were an estimated 3.26 million (95%, uncertainty interval 2.07–3.90) children and adolescents ages 0-18 years living with chronic HCV infection *(69)*. 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 *(69, 70)*. Regardless of age, most children with HCV infection have asymptomatic or minimally symptomatic liver disease, and cirrhosis, hepatocellular carcinoma or extrahepatic manifestations are rare. Yet, recent evidence suggests that those with perinatal exposure developed cirrhosis at an earlier age *(71)*. HCV infection may also decrease the general health and quality of life of adolescents *(72, 73)*. Therefore, early diagnosis and treatment in children is key to preventing long-term morbidity *(74)*.

Prior to regulatory approval of DAAs for use in children, the standard of care of adolescents and children infected with HCV was dual therapy with pegylated-interferon alpha and ribavirin for 24 weeks for genotypes 2 and 3, and 48 weeks for genotypes 1 and 4 *(75-83)*. This combination resulted in an SVR rate of around 52% for HCV genotypes 1 and 4 and 89% for HCV genotypes 2 and 3 *(75, 76, 78, 80)*, but it was associated with significant side-effects. At the time of the 2018 WHO HCV guidelines, none of the recommended pangenotypic DAAs for adults (sofosbuvir/daclatasvir, sofosbuvir/velpatasvir, glecaprevir/pibrentasvir) had been approved for use in either adolescents or children. Therefore, WHO recommended use of two non-pangenotypic DAA regimens (sofosbuvir/ledipasvir and sofosbuvir/ribavirin) that had received regulatory approval from the FDA and the EMA for use in adolescents (≥12 years) *(84, 85)* but advised deferral of treatment in those under than 12 years of age until DAA regimens became available for these younger age groups *(73, 86)*.

Since 2018, the high rate of HCV viral clearance observed in adults with the various pangenotypic DAA regimens has been replicated among adolescents and children. This led to approvals by the key regulatory agencies, the FDA and the EMA. Among adolescents, the pangenotypic regimens, glecaprevir/pibrentasvir, sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir, were approved in 2020 and 2021. Among children ages three years and older, sofosbuvir/ledipasvir was approved in 2019, followed by glecaprevir/pibrentasvir and sofosbuvir/velpatasvir in 2021. Although the sofosbuvir/daclatasvir 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 *(87, 88)*, there is no regulatory approval for this DAA combination, as the originator companies are no longer collaborating *(89)*. Alignment of WHO-recommended DAA regimens across adults, adolescents and children would simplify procurement, promote access to treatment among children in LMICs and help support global elimination efforts.

4.3 Summary of the evidence for treatment in adolescents and children (Web Annex C)

A WHO-commissioned systematic review and meta-analysis of the efficacy and safety of key DAA regimens was undertaken for adolescents (12–18 years), older children (6–11 years) and younger children (3–5 years) with chronic hepatitis C virus infection, based on the same age groupings used in the trials for regulatory approval. There were 49 studies (three RCTS, 28 non-RCTs and 18 observational studies). Together, they reported treatment experience in 1891 adolescents (35 study arms), 472 older children (13 study arms) and 167 younger children (7 study arms). There were no placebo-controlled RCTs, and findings were based on summary estimates of SVR cure rates by regimen in the three age groups. However, these were considered informative because spontaneous clearance is rare in the absence of treatment. Data on serious adverse events and treatment discontinuations were considered more informative than adverse events alone because of the lack of a comparison group. The majority of participants were non-cirrhotic (1786, 70.6%), treatment-naïve (1825, 72.1%), and with non-GT3 infection (1453, 57.4%).

Overall, sustained virological response rates 12 weeks after the end of treatment (SVR12) were high (≥95%) in all age groups and for the key pangenotypic DAA regimens as well as for sofosbuvir/ledipasvir. The rate of any adverse event was higher for children ages 3–5 years (72%) than for those ages 6–11 years (53%) or adolescents (50%), but serious adverse events and treatment discontinuations were uncommon (<1%), except in young children (6.6%) because of the poor palatability of the oral formulation of sofosbuvir/velpatasvir in this group. Less than half of the studies (22/49 (44.9%)) reported information on comorbidities. There were 15 persons with cirrhosis across nine studies, 304 persons who were treatment-experienced across 21 studies and 157 persons with GT3 infection across eight studies. There were no studies of sofosbuvir/daclatasvir in children or adolescents reported from sub-Saharan Africa, where HCV genotype 4 non-a/d subtypes are endemic in some regions, as well as other genotypes (including genotype 1 and 3) that frequently contain resistance-associated substitutions in the NS5A regions. This may contribute to higher rates of treatment failure with sofosbuvir/daclatasvir.

Virologic response rates after treatment were ≥95% in all age groups and for the key pangenotypic DAA regimens.

All studies but two were classified as at low risk of bias.

4.3.1 Adolescents (12–17 years)

Of the 1891 adolescents included in 35 study arms, 183 received sofosbuvir/daclatasvir (the majority for 12 weeks), 102 sofosbuvir/velpatasvir (12 weeks), 47 glecaprevir/pibrentasvir (44 for eight weeks and three for 16 weeks), and 1686 received sofosbuvir/ledipasvir (12 weeks). All were non-cirrhotic; 1167 (52%) had non-genotype 3 infection, and 274 (14%) patients had treatment experience.

SVR12: Overall, SVR12 was 99% (95% CI: 98–100) among the 1891 adolescents, with good tolerability and minimal heterogeneity. SVR12 was 99% (96–100) for sofosbuvir/daclatasvir, 95% (90–99) for sofosbuvir/velpatasvir, 98% (91–100) for glecaprevir/pibrentasvir and 99% *(98-100)* for sofosbuvir/ledipasvir.

Adverse events and treatment discontinuations: Of the studies that reported adverse events, 318 (50%) of the adolescents reported at least one adverse event, but only six were considered serious adverse effects. Only 10 adolescents (0.5%) discontinued treatment.

Strength of evidence: high for sofosbuvir/daclatasvir, moderate for glecaprevir/pibrentasvir and sofosbuvir/ledipasvir, and low for sofosbuvir/velpatasvir. Evidence was downgraded mainly for inconsistency and imprecision.

4.3.2. Older children (6–11 years)

Of the 472 older children included in 13 study arms, 73 received sofosbuvir/velpatasvir (12 weeks), 56 received glecaprevir/pibrentasvir (8, 12 or 16 weeks), 34 received sofosbuvir/daclatasvir (12 weeks) and 178 received sofosbuvir/ledipasvir for 12 weeks. All participants except three were non-cirrhotic; all but seven were treatment-naïve; and the majority were infected with non-genotype 3.

SVR12: Overall, SVR12 was 99% (95% CI: 97–100%) and there was minimal heterogeneity. SVR12 was 100% (94–100) for sofosbuvir/daclatasvir, 93% (86–98) for sofosbuvir/velpatasvir, 96% (90–100) for glecaprevir/pibrentasvir and 100% *(97-100)* for sofosbuvir/ledipasvir.

Adverse events and treatment discontinuations: Of the studies that reported adverse events, 226 (53%) children reported at least one adverse event, but none was rated as serious. four of 490 children (1%) discontinued treatment, which in three children was due to adverse events (auditory hallucinations, drug-related rash, headache).

Strength of evidence: moderate for sofosbuvir/daclatasvir, glecaprevir/pibrentasvir, and sofosbuvir/ledipasvir; and very low for all other DAA treatment regimens evaluated, due mainly to inconsistency and imprecision.

4.3.3. Younger children (3–5 years)

Of the 167 younger children included in seven study arms, 41 received sofosbuvir/velpatasvir (12 weeks), 25 received glecaprevir/pibrentasvir (8 or 12 weeks), and 56 received other regimens. All except one were non-cirrhotic and treatment-naïve. SVR12: Overall, 95% (95% CI: 89–99) attained SVR12, and there was no evidence of heterogeneity. SVR12 was 83% (70–93) for sofosbuvir/velpatasvir, 92% (77–100) but 96% (80-99) for DORA study Part 2) for glecaprevir/pibrentasvir, and 99% (93–100) for sofosbuvir/ledipasvir. There were no study data for sofosbuvir/daclatasvir. The lower SVR12 in those receiving sofosbuvir/velpatasvir was due to seven discontinuations (not virological failure) because of difficulties in taking the oral medication.

Adverse events and treatment discontinuations: Of the studies that reported adverse events, 92 (72%) reported at least one adverse event; the most common were vomiting (21%), cough (14%) and diarrhoea (9%). Treatment discontinuations were rare, but were higher (6.6%) in the sofosbuvir/velpatasvir arms because of relative lack of palatability of the oral formulation.

Strength of evidence: moderate for sofosbuvir/ledipasvir; very low for all other DAAs (sofosbuvir/velpatasvir, glecaprevir/pibrentasvir). There were no data for sofosbuvir/daclatasvir.

There were insufficient studies that reported on outcomes by cirrhosis, genotype and treatment experience. Only three studies reported the HIV co-infection status of participants. There were five HIV co-infected participants, of whom three were treated with glecaprevir/pibrentasvir; all achieved SVR12 *(90-92)*. Overall, the small numbers of HCV-infected children means that subgroup analyses will be limited.

4.3.4 Quality of life assessment

Data from three studies indicate that HCV infection in children has a detrimental effect on quality of life, leading to increased caregiver stress, strain on the family system and poorer health status, including impaired psychosocial and cognitive functioning *(93-95)*. Three other studies explored the impact of DAA treatment on the quality of life of children and adolescents. They showed improvement in health-related quality of life scores after achieving SVR12 *(90, 96, 97)*.

4.3.5 Supporting pharmacokinetic (PK) data for use of 200/30 mg sofosbuvir/daclatasvir in children ages <12 years *(101)*

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

The use of extrapolation to support paediatric drug development is a well-established practice in regulatory approvals *(98)*, whereby efficacy, safety and PK data in young children is extrapolated from adequate studies in adult, adolescents or older children. This applies when the course of the disease or condition and the response to treatment are expected to be similar in children and adults. Modelling and simulation is a critical step in identifying the correct dose, to be confirmed in a targeted PK study. Extrapolation is specifically cited in FDA guidance as appropriate in development of DAAs for children *(67)*. The PK data were used to complement the available clinical data on SVR rates for older children, but they did not change the quality rating.

A PK analysis was undertaken to predict daclatasvir 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 daclatasvir, and to determine the lowest body weight at which children could be treated using these doses. Daclatasvir concentration data from 17 HCV-infected adolescents receiving sofosbuvir/daclatasvir (400 mg/60 mg once daily) who participated in a PK study in Egypt were used for model development *(99,100)* . PK parameters were estimated using a population approach. Monte Carlo simulations were run for virtual children weighing 10 to <35 kg receiving 60 or 30 mg once daily, and daclatasvir exposures were compared with ranges seen in adults. Daclatasvir 30 mg once daily was predicted to achieve effective and safe exposures in children 14 to <35 kg and even down to 10 kg *(101)*. Two complementary studies assessed sofosbuvir pharmacokinetics in children relative to adults to establish appropriate dosing in children. One study evaluated PK of sofosbuvir 200 mg and sofosbuvir/ledipasvir 200 mg/45 mg in children ages 6 to <12 years and weighing ≥17 and <45 kg *(86)*. Sofosbuvir and GS-331007 Area under the curve (AUC) and Cmax in children ages 6 to <12 years were within predefined PK equivalence boundaries of 50–200%. A further open-label study of sofosbuvir/ribavirin in children ages 3–<12 years used sofosbuvir 200 mg (6–<12 years), 200 mg (3–<6 years and ≥17 kg) and 150 mg (3–<6 years and <17 kg)*(102)*. Overall, exposures were comparable to those observed in adults *(103)*, but Cmax was higher *(104)*.

Overall, the data suggest that it would be acceptable to use the existing adult dose of sofosbuvir/daclatasvir (400 mg/60 mg) in children down at least to 25 kg and a half dose (200 mg/30 mg) for those 14–25 kg, potentially down even to 10 kg. Two efficacy, safety and PK studies of sofosbuvir/daclatasvir among children <12 years of age are now planned in Egypt and Cambodia to validate the optimal dosing in the intended paediatric population as the basis for regulatory approval and country adoption.

4.4 Rationale for the recommendations

4.4.1. Balance of benefits and harms

Treat all adolescents and children ≥ 3 years with chronic hepatitis C infection

The Guidelines Development Group made a strong recommendation for treatment of all adolescents and children ages 6–11 years with chronic hepatitis C infection, regardless of stage of disease, based on high/moderate certainty of evidence, and a conditional recommendation for treatment of those ages 3–5 years, based on moderate/very low certainty of evidence in younger children, for the following reasons:

1. **Benefits of earlier treatment in childhood and adolescence** include the possibility of achieving a cure before the onset of disease progression, thus preventing HCV-associated liver damage and extrahepatic manifestations. The overall resulting reduction in transmission will reduce the prevalence and incidence in children and adolescents to achieve an HCV-free generation. 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 reported 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. It also improves neurocognitive dysfunction that affects school performance and quality of life.
2. **Treatment of HCV infected children and adolescents (3–17 years of age) is highly effective and safe,** with SVR12 rates ≥95% in all age groups for the key pangenotypic DAA regimens already recommended for adults (sofosbuvir/daclatasvir, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir). This conclusion is based on high, moderate and low certainty of evidence, respectively, for adolescents and older children and very low certainty for all regimens in younger children.
3. **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, but it may be less in younger children, as they experienced more problems with treatment discontinuations due to poor palatability with some regimens and adverse effects.

Treat adolescents ages 12–17 years and older children ages 6–11 years (weighing at least 35 kg) with sofosbuvir/velpatasvir, glecaprevir/pibrentasvir or sofosbuvir/daclatasvir (Web Annex B).

The Guidelines Development Group recommended that all chronically HCV-infected adolescents and older children should be offered treatment with the current FDA- and EMA- approved pangenotypic DAA regimens of sofosbuvir/velpatasvir and glecaprevir/pibrentasvir, as well as sofosbuvir/daclatasvir, previously recommended in adults, based on the following rationale:

1. Both direct evidence from a systematic review and meta-analysis of use of these DAA regimens in 1891 adolescents (12–18 years of age) from 35 studies and 472 older children (6–11 years of age) from 13 studies confirmed high efficacy, safety and tolerability, as did indirect evidence from adult treatment studies for all DAA regimens.
2. The PK modelling data suggest that it should be possible to use the existing adult dose of sofosbuvir/daclatasvir (400 mg/60 mg) in children down at least to 25 kg.
3. This new recommendation replaces ribavirin which requires haematological monitoring, with the use of sofosbuvir in adolescents. Also, ribavirin is a teratogenic agent and contraindicated in pregnancy. This is particularly relevant, as adolescents' pregnancies are more likely to be unplanned.
4. Data on treatment in those with cirrhosis remains limited, but recommendations include those with compensated cirrhosis. In those who are treatment-experienced and with compensated cirrhosis, treatment for 24 weeks is recommended.

Treat children ages 3–5 years

The 2018 HCV guidelines recommended that treatment be deferred in young children until they either reach 12 years of age or DAA regimens were approved for those under 12 years of age. This recommendation was based largely on the low frequency of HCV-related liver disease in childhood and the significant side-effects of interferon alpha – some irreversible *(79, 80, 105-109)* – and overall low efficacy, prolonged treatment duration (6–12 months), inconvenient administration route (via injection) and high costs. It was recommended that interferon-based regimens should no longer be used for either adolescents or children.

The Guidelines Development Group recognized that the benefits of treatment with DAAs (sofosbuvir/velpatasvir, glecaprevir/pibrentasvir, sofosbuvir/daclatasvir) likely outweigh those of deferral even in those less than six years of age, who are at low risk of advanced liver disease *(110, 111)*. A conditional recommendation was made to initiate DAA treatment in children ages 3–5 years based on the following rationale:

1. Curative short-course oral pangenotypic DAA regimens (sofosbuvir/velpatasvir, glecaprevir/pibrentasvir) as well as also sofosbuvir/ledipasvir now have regulatory approval for children down to three years of age.
2. There was high efficacy and no major safety concerns across these regimens – sofosbuvir/velpatasvir and glecaprevir/pibrentasvir based on direct studies and sofosbuvir/daclatasvir based on extrapolation from studies in adolescent and older children.

3. Overall, the data suggest that it should be possible to use the existing adult dose of sofosbuvir/daclatasvir (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, potentially down even to 10 kg.
4. For sofosbuvir/daclatasvir, the modelling exercise based on PK data in adolescents indicated that half of the adult dose (that is, 200 mg/30 mg) could be used for children weighing 14–25 kg and potentially down even to 10 kg. As noted above, the use of extrapolation to support paediatric drug development is a well-established practice in regulatory approvals *(98,112)*, whereby efficacy, safety and PK data in young children can be extrapolated from adequate studies in adult, adolescents or older children. Extrapolation can be applied when the course of the disease or condition and the response to treatment are expected to be similar in children and adults and matching drug exposure in children to the safe and effective exposure in adults reliably predicts successful treatment. This situation meets all key conditions that support extrapolation of the efficacy observed in adults receiving sofosbuvir/daclatasvir. A PK/efficacy and safety study will be conducted in children to confirm that the proposed dose provides exposure similar to that shown to be safe and effective in adult patients.

4.4.2 Values, preferences and acceptability (Web Annex D)

The assessment of the Guidelines Development Group was that, given the marked benefits relative to harms, the recommendations were not sensitive to preferences.

An online survey was distributed between August and September 2021 to global, regional and national networks of paediatricians treating HCV-infected children and adolescents. The survey assessed preferences and acceptability regarding which children to treat and prioritize and which DAA regimens to use. Networks included: PENTA Child Health network and the Federation of International Societies of Paediatric Gastroenterology, Hepatology and Nutrition (FISPGHAN) and its regional counterparts – the Asian Pan-Pacific Society (APPSPGHAN); the Commonwealth Association of Paediatric Gastroenterology and Nutrition (CAPGAN); the European Society (ESPGHAN); the Latin American Society (LASPGHAN); the North America Society (NASPGHAN); and the Pan Arab Society (PASPGHAN). Some 142 health care workers responded, of whom 94 had treated HCV-infected for children or adolescents in the preceding three years. All WHO geographic regions were represented among respondents; the highest proportions of respondents were from the Western Pacific (43%) and the Americas (19%). It was not possible to survey end-users such as parents, care-givers or the children themselves, as there is still very limited routine testing and case-finding of children, and therefore most parents would be unaware their child is infected. Even fewer have experience of their child being treated.

Preferences for treating different age groups: 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; but 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 majority of respondents (59%) supported inclusion of treatment recommendations in the guidelines for children 3 years of age and older. A further 15% supported inclusion of treatment recommendations only for older children (≥6 years) and adolescents, and 22% supported treatment for adolescents only.

Preferences for choice of regimen: The most commonly used and preferred DAA regimens for treatment across all age groups among 82 health care workers who reported recent treatment experience were: sofosbuvir/ledipasvir (52% for adolescents and 28% for older children); sofosbuvir/velpatasvir (32% for adolescents and 20% for older children); and glecaprevir/pibrentasvir (23% for adolescents and 10% for older children). The main reason for their use, given by 95% of respondents, was drug availability, because they were the most commonly available regimens at the respondents' facilities. Other reasons included: good safety data (95%), professional society guidelines recommending their use (88%), suitability of a regimen to treat HCV genotypes prevalent in the country (including pangenotypic) (84%) and high efficacy (72%).

Although there was no commissioned survey of end-users – that is, either parents or HCV-infected children/adolescents, previous surveys have indicated that curative, short-course (that is, 8–12 weeks) oral DAA treatment is highly acceptable to adolescents and children, as well as to their parents or caregivers *(96)*, because of the high likelihood of a cure, and minimal adverse events compared with interferon injections. Cure will enable adolescents and children to live free of a socially stigmatizing infection. It is recognized that some younger children may have issues with palatability, especially if the medication is available only in tablet form, as is sofosbuvir/daclatasvir.

4.4.3 Equity

The approval of DAAs for use in adolescents and younger children is a major opportunity to advance treatment access and cure to a vulnerable group that will benefit from early treatment. With an estimated 3.26 million children living with chronic HCV infection globally, national elimination of HCV will not be achieved unless children and adolescents are also tested and treated *(113)*. There will be a need to ensure equitable access to recommended DAAs for all HCV-infected children and adolescents, including adolescents from stigmatized populations, such as people who inject drugs and men who have sex with men.

National elimination of HCV will not be achieved unless children and adolescents are also tested and treated.

4.4.4 Feasibility

The systematic review reported treatment experience among 2906 adolescents and children (2228 adolescents (12–18 years), 472 older children (6–11 years), 167 young children (3–5 years)) using a wide range of DAA regimens, including sofosbuvir/velpatasvir; sofosbuvir/daclatasvir, glecaprevir/pibrentasvir, and sofosbuvir/ledipasvir. Overall, efficacy was reported to be high, and no major adverse effects were reported. The two originator products, sofosbuvir/velpatasvir and glecaprevir/pibrentasvir, received regulatory approval in 2021 for use among children down to the age of three years. For sofosbuvir/daclatasvir, results from pharmacokinetic modelling suggest that the existing adult dose of 400 mg/60 mg in children down at least to 25 kg, and a half dose (200 mg/30 mg) for those 14–25 kg, would achieve safe and effective exposures for the commonly reported genotypes worldwide, but evidence on genotypes such as 4r, common in some sub-Saharan countries, is uncertain *(43, 54)*. 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 *(114)*.

4.4.5 Resource and access considerations

DAA treatment in adults has been consistently reported as highly cost–effective and cost-saving. There are no published data on paediatric drug costs for LMICs, and no formal cost–effectiveness analyses have been undertaken. In general, treatment of adolescents and younger children may avoid the higher costs associated with treating adults with advanced liver disease and related complications. But costs for procurement of paediatric-specific doses are likely to be higher because of the lower volumes.

Market size: Approximately two thirds of the estimated 3.2 million HCV-infected adolescents and children are those (generally >25 or 30 kg) who 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 aged 6–11 years *(62)*. Specific paediatric dosage forms are more expensive than adult tablets if a new formulation (that is, new composition or dose) is required, due to a smaller commercial market that attracts little interest from generic suppliers. The most efficient path to generic paediatric dosage forms is to scale down adult products already available, either using scored tablets or half dose separate tablets. Gilead and AbbVie received US FDA approval in the second quarter of 2021 for the use of sofosbuvir/velpatasvir and glecaprevir/pibrentasvir among children down to the age of three years. However, these originator products are expensive and unlikely to be available at the scale needed to treat children in LMICs. For some of the rarer HCV genotype 4 non-a/d subtypes, which are endemic in some regions of sub-Saharan Africa, as well as other genotypes elsewhere (including genotypes 1 and 3) that frequently contain resistance-associated substitutions in the NS5A regions, sofosbuvir/velpatasvir is more efficacious in adults.

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

1. **Availability:** Sofosbuvir/daclatasvir is the most widely available and low-cost pangenotypic DAA regimen, available as a FDC and as separate generic products for treatment of adults with chronic HCV infection in LMICs.
2. **Equivalent safety and efficacy:** In LMICs sofosbuvir/daclatasvir, as either the two separate products or the FDC, is equally safe and efficacious as sofosbuvir/velpatasvir and glecaprevir/pibrentasvir for the common genotypes 1 and 4. There remains the possibility of treatment failure of sofosbuvir and daclatasvir with certain genotypes, namely HCV genotype 4 non-a/d subtypes, as well as other genotypes (including genotype 1 and 3) that frequently contain resistance-associated substitutions in the NS5A regions *(43, 54)*.
3. **Pharmacokinetic modelling data:** Modelling results suggest that use of a dosage of daclatasvir 30 mg and sofosbuvir 200 mg – half the adult dose – will provide appropriate drug exposure among younger children.
4. **Availability of generic products:** At present, most DAAs that could be used in children are not available as WHO pre-qualified generic products (Table 4.3). This includes sofosbuvir 200 mg (or 100 mg) tablets, sofosbuvir/velpatasvir low-dose tablets or pellets and glecaprevir/pibrentasvir tablets or pellets. There is currently only a single pre-qualified generic product for sofosbuvir/velpatasvir and none yet for glecaprevir/pibrentasvir. WHO pre-qualified daclatasvir 30 mg is available from multiple generic suppliers and could be used in younger children. However, sofosbuvir in either 100 mg or 200 mg dosage form to pair with daclatasvir is not yet available, and strong advocacy is needed urgently to promote development of a 100 mg sofosbuvir dosage. Sofosbuvir 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). Daclatasvir 30 mg has included on this list since 2016.
5. **Cost:** Sofosbuvir/daclatasvir 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 *(62)*.
6. **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.

TABLE 4.3 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 (FPPSs) That Have Received WHO prequalification.2022. Accessed June 15, 2022. https://extranet.who.int/pqweb/medicines/prequalified-lists/finished-pharmaceutical-products.

WHO Essential Medicines List for Children: All the recommended DAA regimens for children and adolescents (sofosbuvir/daclatasvir, sofosbuvir/velpatasvir and glecaprevir/pibrentasvir) were included in the 2021 update to the WHO Essential Medicines List for Children (EMLC), which is the guide for national lists of essential medicines for children *(115)*.

4.5 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, but recognizing that the caregivers differ.

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.

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 are 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 for adolescents and children and

for treatment of adolescents in their national guidelines, based on the recommendations of the 2017 WHO HCV testing guidelines *(4)*. 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. It may also include screening of pregnant women in countries with high prevalence/burden with policies for linkage to care and follow-up of infants.

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 4.1 describes potential testing opportunities to improve hepatitis case-finding among infants and children. 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 *(114)*. 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.

BOX 4.1 Testing approaches to improve hepatitis case-finding among infants and children

- Prioritize testing children of all HBV- or HCV-positive mothers (especially if the mother is HCV/HIV-coinfected) through home- or facility-based testing.
- Consider offering viral hepatitis testing to all children and adolescents attending HIV services, STI clinics and TB clinics or admitted to hospitals in high prevalence regions.
- Offer viral hepatitis testing or retesting to mothers or infants in maternal and child health services, immunization clinics or under-5 clinics.
- Focus HCV testing on children who have had medical interventions or received blood products in countries with a higher prevalence of hepatitis C or where screening of blood is suboptimal or where medical equipment is inadequately sterilized.
- 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.

- **Provision of care and treatment by non-specialists:** Non-specialist paediatricians can treat HCV-infected children and adolescents. However, although DAA-experienced HCV-infected children and adolescents and those with cirrhosis are rarely encountered in clinical practice, such cases may be most appropriately managed under the supervision of a paediatric specialist. Data that speak to this are few.

- **Paediatric formulations for young children:** Current options include originator product formulations for glecaprevir/pibrentasvir (pellets) and sofosbuvir/velpatasvir (granules) or existing adult 30 mg daclatasvir and 200 mg sofosbuvir tablets. (See section 4.4.5. Resource and access considerations.)
- **Service delivery for adolescents**
  - **Delivering adolescent-friendly services:** Providing services for adolescents require approaches that are adolescent focussed on and friendly to adolescents. WHO has developed standards for delivering quality services for adolescents *(116)*. 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, with an absence of financial barriers, offer flexible opening hours and/or walk-in or same-day appointments. Separate hours and special events for adolescents may help overcome concerns that relatives or neighbours will see them seen attending viral hepatitis/HIV services.
  - **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 or who are using/injecting drugs, those in multiple or concurrent sexual partnerships and those who are sexually exploited or trafficked *(25)*. 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 age of consent can pose a barrier to adolescents' access to HIV and viral hepatitis testing *(117)*. 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. WHO also recommends that children and adolescents themselves be involved in the testing decision as much as possible *(117)*. Countries should revise their age of consent policies in line with best practices, in the best interest of adolescents and in recognition of the heterogeneity and varying levels of maturity among adolescents.
  - **Disclosure:** Adolescents may particularly need support with when and to whom to disclose a positive status *(117)*. When appropriate, and only with the adolescent's specific permission, health care personnel should engage the support of adults – family members, teachers and other community members. Adolescents should be counselled about the potential benefits and risks of disclosure of their HIV or HCV status to others and empowered and supported to determine if, when, how and to whom to disclose.

4.6 Research gaps

Research is particularly needed in the following areas:

- Direct evaluation of sofosbuvir/daclatasvir in children aged 3–5 years and 6–11 years and <25 kg for SVR12, adverse events, tolerability and pharmacokinetics. There is also a need to establish the efficacy of sofosbuvir/daclatasvir in regions where genotypes, including genotypes 1, 3 and 4-non-a/d subtypes, with inherent resistance-associated substitutions that increase treatment failure rates with this regimen are prevalent. In addition, sofosbuvir/daclatasvir pharmacokinetic data are modelled only against wild type, and dose-related efficacy against genotypes 1, 3 and 4-non-a/d subtypes variants in children is uncertain.
- For forecasts for procurement needs, country serosurvey data to inform updated estimates of prevalence and burden in adolescents and children.
- Implementation research studies 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, prior treatment experience, genotype 3 infection, HIV coinfection, and renal impairment.

Current available pangenotypic DAAs for the treatment of HCV- infected persons with compensated cirrhosis

BOX 4.2 Summary of evidence for use of pangenotypic DAA regimens in adults from 2018 HCV guidelines *(1)*

Evidence that pangenotypic DAAs are effective in HCV infection

A WHO-commissioned systematic review identified 142 clinical studies that evaluated the safety and efficacy of various FDA- and EMA-approved DAA regimens. These included sofosbuvir/velpatasvir, glecaprevir/pibrentasvir, sofosbuvir/daclatasvir, daclatasvir/asunaprevir, elbasvir/grazoprevir, ledipasvir/sofosbuvir, paritaprevir/ritonavir/ombitasvir/dasabuvir, sofosbuvir/velpatasvir/voxilaprevir, sofosbuvir/daclatasvir/ribavirin, sofosbuvir/ribavirin. The complete evidence summaries for each of the regimens can be found in Web Annexes of the 2018 guidelines, with a short summary below.

Pangenotypic DAAs in HCV-infected adults without cirrhosis

Sofosbuvir/velpatasvir

In combined treatment-naive and treatment-experienced persons treated with sofosbuvir/velpatasvir, the pooled SVR rates exceeded 96% (92–100%) for all six major genotypes, except for genotype 3 (SVR rate: 89%, 85–93%).

Glecaprevir/pibrentasvir

In combined treatment-naive and treatment-experienced persons treated with glecaprevir/pibrentasvir, pooled SVR rates exceeded 94% (89–100%) for infections with all six major genotypes. For the relatively rare genotype 5, two persons treated reached SVR.

Sofosbuvir/daclatasvir

In combined treatment-naive and treatment-experienced persons treated with sofosbuvir/daclatasvir, the pooled SVR rates exceeded 92% for infection with genotypes 1, 2, 3 and 4. Data from an observational study (manuscript in preparation, MSF demonstration project) provided information on the less commonly reported genotypes 5 and 6. A total of eight persons with genotype 5 and 123 persons with genotype 6 infection were treated with sofosbuvir/daclatasvir for 12 weeks. SVR rates were, respectively, 88% and 94% for genotypes 5 and 6.

Pangenotypic DAAs in HCV-infected adults with compensated cirrhosis

Sofosbuvir/velpatasvir

In combined treatment-naive and treatment-experienced persons with cirrhosis treated with sofosbuvir/velpatasvir for 12 weeks, the pooled SVR rates in those infected with genotypes 1, 2 and 4 were 90%, 86% and 88%, respectively. The pooled SVR rate in genotype 3 infection was 97% in treatment-naive persons and 90% in treatment-experienced persons. An additional study (published after the systematic review inclusion period ended) *(108)* reported SVR rates of 100% for both genotype 5 (N= 13) and genotype 6 (N = 20) after 12 weeks of treatment.

Glecaprevir/pibrentasvir

In combined treatment-naive and treatment-experienced persons with compensated cirrhosis treated with glecaprevir/pibrentasvir for 12 weeks, SVR rates exceeded 94% for infection with genotypes 1, 2, 3, 4 and 6. Two persons treated for infection with genotype 5 reached SVR.

Sofosbuvir/daclatasvir

In combined treatment-naive and treatment-experienced persons with compensated cirrhosis treated with sofosbuvir/daclatasvir for 12 weeks, the pooled SVR rates exceeded 93% for infection with genotypes 1 and 2. SVR rates for infection with genotype 3 were low, ranging from 79% to 82%. However, after 24 weeks of treatment , SVR rates increased to 90%. Data from an observational study (manuscript in preparation, MSF demonstration project) provided information on genotypes 5 and 6, and real-world data from Egypt provided information on genotype 4 *(118)*. One cirrhotic person with genotype 5 infection treated with sofosbuvir/daclatasvir for 12 weeks reached SVR. Among 185 cirrhotic persons with

genotype 6 infection treated with sofosbuvir/daclatasvir for 12 weeks, 92% reached SVR. Cirrhotic persons with genotype 4 infection had SVR rates that exceeded 98% after 12 weeks of treatment *(118)*.

Safety of pangenotypic DAAs

Treatment discontinuation due to adverse events was very low in persons without and with cirrhosis in the regimens discussed above (<1%). Similar results were observed in treatment-naive and treatment-experienced persons.

Rationale for the recommendation

The Guidelines Development Group made an overall recommendation to use pangenotypic DAA regimens for the treatment of HCV infection. The Group acknowledged that the potential clinical benefits of pangenotypic regimens are similar to those of non-pangenotypic regimens. However, pangenotypic DAAs present an opportunity to simplify the care pathway by removing the need for expensive genotyping and so simplifying procurement and supply chains. These regimens offer a major opportunity to facilitate treatment expansion worldwide.

The Guidelines Development Group acknowledged that there are countries where pangenotypic formulations may not yet be approved or available. In addition, there are countries where the HCV epidemic is almost entirely caused by one genotype, and where national hepatitis programmes successfully use a non-pangenotypic DAA regimen such as sofosbuvir/ledipasvir. In these cases and when treating adolescents, there remains a role for non-pangenotypic DAAs while national programmes transition to using pangenotypic regimens.

Balance of benefits and harms

The use of pangenotypic regimens removes the need for genotyping. This simplifies medicine procurement and supply chains, may reduce costs and loss to follow up after diagnosis. Potential harms include the development of rare long-term side-effects of these recently approved medicines, which may not have been identified during post-marketing surveillance, and the potential overtreatment of persons treated with sofosbuvir/daclatasvir if persons are treated for 24 weeks in the absence of genotyping.

Values and preferences and acceptability

Four identified studies investigated the preferences of HCV-infected persons regarding HCV treatment regimens. For persons infected with HCV, the likelihood of a cure and the lack of adverse events are the most important considerations related to treatment regimens, though factors such as a shorter (e.g. 8-week) course of treatment were also valued (97–100). Therefore, use of pangenotypic regimens would be acceptable.

Resource considerations

The resources required to administer HCV therapy can be broadly divided into health system costs (e.g. laboratory and personnel) and the price of medicines. Treating persons with pangenotypic DAAs incurs fewer health system costs as it removes expensive genotyping, which requires specialist laboratories and personnel, saving up to US$ 200 per test in LMICs. The Guidelines Development Group recognizes, however, that access to pangenotypic DAA regimens remains limited in many LMICs. Prices for sofosbuvir/velpatasvir and glecaprevir/pibrentasvir are still higher than the older DAA combinations, but it is expected that prices will substantially decrease as the volume of use increases and access policies for HCV-infected persons living in LMICs are optimized.

Feasibility

The WHO 2020 progress report on access to hepatitis C treatment points to the feasibility of widening access to HCV treatment with the use of pangenotypic DAAs *(55)*.

Equity

Simplifying the care pathway by using pangenotypic regimens could improve equity and help improve access to populations that currently do not have access to HCV treatment.

SIMPLIFIED SERVICE DELIVERY FOR A PUBLIC HEALTH APPROACH TO HCV TESTING, CARE AND TREATMENT

CHAPTER 5. DECENTRALIZATION AND INTEGRATION

5.1 Recommendations: decentralized and integrated HCV testing and treatment services

New recommendations

Decentralization:[1] 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.
(strong recommendation; certainty of evidence[2] moderate (people who inject drugs, prisoners); low (general population, people living with HIV))

Integration:[3] 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), prisons and HIV/ART services.
(strong recommendation; certainty of evidence: moderate (people who inject drugs, prisoners); low (general population, people living with HIV))

[1] Decentralization of services refers to service delivery at peripheral health facilities, community-based venues and locations beyond hospital sites or traditional health care settings, bringing care nearer to patients' homes.

[2] The systematic review was based on an analysis by population group (people who inject drugs, prisoners, general population and people living with HIV) rather than setting or services (harm reduction sites, prisons, primary care or HIV/ART clinics), although these were highly related to population group.

[3] Integrated service delivery refers to delivery of different health services in a way that ensures people receive a continuum of health promotion, disease prevention, diagnosis and treatment.

5.2 Background

In 2016, WHO developed the global health sector strategy on viral hepatitis 2016–2021 *(10)*, with a goal of eliminating viral hepatitis as a public health threat by 2030. Elimination was defined as a reduction in hepatitis-related mortality by 65% and in incidence of chronic infections by 90%. Advances in treatment and diagnostics as well as price reductions and WHO guidelines recommendations in 2018 for a "treat all" approach regardless of stage of disease, using a few pan-genotypic regimens *(1)*, have transformed the global response to and feasibility of eliminating HCV infection *(119)*.While impressive progress has been made in several Member States, major

testing and treatment gaps remain. As of 2019, only a small proportion of persons with chronic HCV infection have been diagnosed (21%) and even fewer, treated (13%) *(9)*. Reaching the 90% testing and 80% treatment coverage targets will require a substantial simplification in service delivery. Until recently, delivery of viral hepatitis testing and treatment in many countries relied on models of specialist-led centralized care in hospital settings *(120, 121)*. Even when testing was undertaken at the community level, there was often significant attrition, as patients needed to attend a different hospital service for confirmatory HCV RNA testing and treatment *(122-124)*.

Reaching the 90% testing and 80% treatment coverage targets will require a substantial simplification in service delivery.

Decentralization: Decentralization of services refers to service delivery at peripheral health facilities, community-based venues and locations beyond hospital sites, bringing care nearer to patients' homes. Most of the evidence to inform simplified approaches such as decentralization of care to primary care facilities and task sharing with nurses, non-specialist doctors as well as peers is based on the HIV literature *(8)*. Decentralization of HIV treatment services was a key factor in successful global scale-up, improving uptake of both testing and treatment and reducing loss to follow-up *(125, 126)*. It was also shown to reduce transportation cost and waiting time experienced at central hospitals. As a result, decentralization improves linkage to treatment and follow-up. It can also strengthen community engagement by linking community-based interventions with health facilities and optimize access to services, care-seeking behaviour and retention in care *(127-130)*. In 2021 WHO made a conditional recommendation for initiating ART outside health facilities to reduce delays in starting treatment *(2)*.

Integration of HCV testing, care and treatment with existing services: WHO already recommends integration of hepatitis C testing into a range of other clinical services, such as services for TB, HIV/ART, maternal and child health, screening for noncommunicable diseases, sexual and reproductive health (especially STI clinics), mental health, harm reduction programmes, migrant and refugee services and in prisons *(2, 3)*. The primary purpose of integration and such programme collaboration is to create integrated delivery systems that can facilitate access to hepatitis testing and treatment along with other health services. By making hepatitis B and C testing and treatment more convenient for people coming to health facilities it can expand the reach and uptake of viral hepatitis care. Also, for the HCV-infected person, integration of hepatitis testing into other health services may facilitate addressing other health needs at the same time, thereby saving time and money. For the health system, integration may reduce duplication of services and improve coordination (for example, in stock management of diagnostic assays) and linking reporting systems to share information between settings and providers.

In the 2018 update to the WHO HCV guidelines *(1)*, WHO described eight key good practice principles to simplify service delivery across the continuum of care and support implementation of the "Treat All" recommendations (Box 5.1). There is now substantial evidence supporting three key interrelated components of HCV simplified service delivery –decentralization of services from specialized centres, integration of hepatitis testing, care and treatment with other, existing services, and task sharing to non-specialist health care workers) – to inform updated WHO recommendations.

The three chapters in this section provide updated recommendations on decentralization to peripheral health facilities: integration of HCV testing and treatment with other services (Chapter 5); and task sharing to non-specialists (Chapter 6); followed by a summary of all strategies to promote uptake of testing and linkage to care and treatment (Chapter 7). These should be considered alongside the existing good practice principles in the following areas: comprehensive national planning, simple and standardized algorithms, differentiated care strategy, community engagement and peer support, strategies for more efficient procurement and supply management, and data systems to monitor the quality of individual care and coverage.

BOX 5.1 Good practice principles for HCV health service delivery, from the 2018 *Guidelines for treatment of persons diagnosed with chronic HCV infection (1)*

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 and human resources.
2. Simple and standardized algorithms across the continuum of care from testing through 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 to increase the efficiency and reach of hepatitis services. New recommendation
5. Decentralized testing and treatment services at primary health facilities or harm reduction sites to promote access to care. New recommendation
6. Task sharing, supported by training and mentoring of health care workers and peer workers. New recommendation
7. Differentiated care strategy to assess needs at different levels of carte, with specialist referral as appropriate for those with complex problems.
8. Community engagement and peer support to promote access to services and linkage through the continuum of care, which includes addressing stigma and discrimination.
9. Strategies for more efficient procurement and supply management of quality-assured, affordable medicines and diagnostics.
10. 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.

5.3 Summary of evidence (Web Annex C)

Previous systematic reviews of decentralized HCV service delivery models *(131–138)* included few studies from LMICs, focused on older treatment regimens and did not examine all outcomes across the HCV care cascade. Now, a WHO-commissioned systematic review and meta-analysis of 142 studies (489 996 persons) from 33 countries (20 studies (14%) were in LMICs) has examined the effectiveness of key simplified service delivery interventions – decentralization, integration, and task sharing to non-specialists – on outcomes across the HCV cascade of care (uptake of HCV serologic testing, nucleic acid testing (NAT), treatment, cure assessment and SVR12 (cure) *(139)*. Studies were grouped and analysed by four distinct populations: 80 (56%) studies were among people who inject drugs, 20 (14%) were among people in prisons, five (4%) involved people living with HIV, and 37 (26%) were conducted in the general population. Some 123 studies (87%) were single-arm, and 11 (8%) were comparator observational studies. There were only six RCTs. Most studies (61%) reported only data on treatment outcomes, but 38 studies (27%) covered outcomes across the full HCV continuum of care, that is, both testing and treatment outcomes. Of the 154 arms included in the decentralization analyses, 88 arms (181 398 persons) reported outcomes associated with full decentralization and/or integration (that is, both testing and treatment delivered at peripheral health facility and/or integrated with existing services), 44 arms (14 935 persons) reported outcomes associated with partial decentralization and integration (that is, testing delivered at peripheral health facilities and integrated with existing services but with referral for treatment elsewhere), and 22 arms (666 persons) reported outcomes where there was no decentralization or integration, that is, testing and treatment at tertiary care facilities. Regarding risk of bias, 9% of studies had critical risk of bias, 35% had serious risk of bias, and 27% had moderate risk of bias. Only 29% had low risk of bias; these were mostly studies in the general population.

Among people who inject drugs, there was higher HCV RNA NAT testing uptake for full decentralization/integration at harm reduction sites than with partial decentralization or no decentralization (ND): respectively, 98% (95% CI 95–100%) versus 81% (69–91%) versus 82% (13–100%), and higher DAA treatment uptake levels: respectively, 73% (63–80%) versus 66% (55–77%) versus 35% (23–48%). Similarly, for those in prison settings, there was higher linkage to care with full decentralization and integration into existing prison services versus partial decentralization: 94% (79–100%) versus 50% (29–71%) and higher DAA treatment uptake: 72% (48–91%) versus 39% (17–73%).

For general populations, with decentralization and integration of HCV testing and treatment into primary care services, there was a high degree of heterogeneity and overlapping confidence intervals in outcomes for HCV RNA viral load uptake, linkage to care and treatment uptake. The proportion of patients achieving cure (SVR12) was high (>95%) across all levels of decentralization/integration and for all populations.

The findings among people who inject drugs were confirmed in studies with comparator arms, which found higher linkage to care and treatment uptake for full decentralization/integration of HCV testing and treatment at harm-reduction sites versus no decentralization/integration: 88% (77–94%) versus 67% (54–78%) (p=0.008) and 88% (65–100%) versus 33% (25-43%) (p<0.001), respectively. Overall, results were similar across seven studies with comparator arms and non-comparator studies.

The key limitations of the review were that it was based largely on single-arm observational studies with different levels of decentralization. Only 13 studies (9%) had a comparator arm, and only four were RCTs that made possible a direct comparison of different levels of decentralization and integration. There was Also, studies from LMICs were under-represented, and studies with data from the early testing and linkage part of the cascade were compared with the later treatment steps in the treatment cascade. Many studies also included other interventions addressing different steps in the care cascade – for example, use of POC HCV RNA assays, reflex laboratory-based viral load testing, patient navigators or peer workers – alongside decentralization or integrated care, which may have affected outcomes.

5.3.1 Additional supporting evidence from HIV literature for decentralization and integrated care

Findings from the HIV literature on decentralization also show comparable rates of viral suppression on ART as well as increased uptake of testing and treatment with full decentralization (for example, community-based HIV testing and treatment at lower-level health facilities) *(135, 140–143)*. The HIV ART literature also demonstrates the beneficial impact of providing integrated HIV care for people who inject drugs *(144–146)*. The convenient co-location of HIV testing and treatment integrated with OAMT services or primary care/community sites where multiple needs can be met in one easily accessible setting has been an important facilitator of access to care for people who inject drugs *(146–148)*. WHO currently recommends offering HIV care and ART at OAMT sites *(146)*.

WHO already recommends integration of HIV testing and ART treatment into a range of other clinical services, such as services for TB, HIV/ART, maternal and child health, sexual and reproductive health (particularly STI clinics), OAMT programmes, migrant and refugee services, and in prisons *(2)*. The same integration of services should extend to hepatitis C and B.

5.4 Rationale for the recommendations

The Guideline Development Group made a strong recommendation for adoption of fully decentralized HCV testing and treatment at the same peripheral health care facility and for full integration into existing services. This recommendation was based on evidence of moderate certainty of increased uptake of HCV viral load testing, linkage to care, and treatment at harm reduction sites among people who inject drugs, as well as among prisoners in closed settings, and evidence of low certainty among the general population in primary care settings.

5.4.1 Overall balance of benefits and harms

The key benefits of expanding delivery of HCV services beyond tertiary or specialist facilities to fully decentralized, co-located and integrated HCV testing and treatment services at the primary and secondary care levels, harm reduction services, prisons and HIV clinics include the following:

1. Such expansion will increase access to HCV testing and treatment services and so accelerate progress towards elimination.

2. Delivery of HCV testing, care and treatment ideally as a "one-stop-shop" nearer to the patient will also be more convenient, with fewer visits and so potential for reduced transport costs and less time off work.

3. Co-location of testing and treatment services can be integrated with either harm reduction services or with primary care services, prison services or HIV/ART clinic, where multiple needs can be met in one easily accessible setting.

4. The impact on access of a decentralized, co-located "one-stop shop" for HCV testing and treatment will be greatest among people who inject drugs, who have particular difficulties accessing health services and have high rates of loss to follow-up. Many studies now show the feasibility of improving access to diagnosis and treatment among the marginalised and hard-to-reach people who inject drugs and prisoner populations through delivery of integrated care. Surveys of end-users suggest that delivery of HCV testing and treatment at harm reduction sites is associated with less stigma and as a result promotes access.

5. For the health system, integration may reduce duplication of services and improve coordination (for example, in stock management of diagnostic assays) and linking reporting systems to share information between settings and providers.

The key challenges with decentralization *(148, 149)* are that there is usually less specialist expertise at decentralized site, and a good triage system is needed to ensure those in need of more specialist care are identified and referred. Decentralization of HCV testing and treatment and integration with existing primary care may therefore require additional training for health care workers to ensure delivery of client friendly services, particularly for marginalized groups,

such as people who inject drugs, and safe treatment for individuals with potentially advanced disease and greater risks of adverse events. The Guidelines Development Group considerd that the benefits considerably outweighed any potential harms.

5.4.2 Cost and cost–effectiveness

Four studies have evaluated the cost–effectiveness of different levels of decentralization and task sharing *(150–153)*. A general population study by Médecins Sans Frontières (MSF) compared a simplified decentralized treatment and care model with a full model of care *(153)*. They calculated costs per quality-adjusted life year (QALY) gained for each model of care based on a mathematical modelling of real-world treatment programme data. The full model of care achieved slightly more QALYs per capita (8.75 versus 8.72) than the simplified model but was much more expensive for each patient – US$ 925 versus US$ 376. A further MSF study among people living with HIV in Myanmar compared a simplified treatment and care model that incorporated task sharing with the existing, full model of care. The full model of care cost over US$ 6000, compared with US$ 5000 for the simplified model, which, assuming similar outcomes, was considered to be cost–effective *(150)*.

A study in Australia examined the integration of HCV treatment and care into community-based care delivered by general practitioners and found that the integrated care improved health outcomes and reduced costs by Australian $42122 per patient, compared with the cost of usual, non-integrated care delivered by specialists (AU$ 64 025) *(151)*. A further modelling study from Australia compared costs and QALYs according to who delivered testing and treatment and found that groups followed by a general practitioner or a combination of a specialist and a nurse resulted in lower costs and better outcomes than those just followed by a specialist *(152)*.

5.4.3 Acceptability, values and preferences (Web Annex D)

Three related surveys or series of in-depth interviews were undertaken among different populations affected by HCV to inform an understanding of the values, preferences and acceptability of different ways of simplifying delivery of care and treatment for chronic HCV infection (that is, decentralization, integration and task sharing of HCV services). Overall, there was strong support for fully decentralized and integrated HCV services offering testing and treatment at the same community site and near to people's homes rather than in hospitals. The importance of a non-judgmental/non-stigmatizing approach among health care providers was highlighted, especially by people who inject drugs and people living with HIV.

Potential service users and health care providers expressed strong preferences for services provided by community-based organizations.

Multi-country online survey (World Hepatitis Alliance and Coalition Plus) (Web Annex D)

Some 210 people in 49 countries participated anonymously in an online survey. Of these, 56% were male, and 71% were between 26 and 55 years old; 23% were living with HCV; 21% were people who formerly injected drugs; 18% identified as "people who inject drugs"; and 16% were living with HIV. Overall, the survey results showed strong support for decentralized and integrated HCV services as well as task sharing. When participants were asked, "Where you would like to test?", the most common responses were: "at a community-based site" (44%) and "at a place of my choice using a self-test" (35%), rather than at a hospital (28%) or primary care (general practice) clinic (28%). Similarly, when asked, "Regardless of your treatment status (treated, not treated), where would you like to receive your treatment?", the most popular sites were "community-based organization centre" (50%), followed by hospital (39%) and general practitioner (29%). Among people who formerly or currently inject drugs, the preferences for testing and treatment at a "community-based organization site" or a "drug user support centre" were even stronger (50%). Overall, the most important reasons given for their choice of testing and treatment locations were "being close to their home or office" (53% and 56%), "reduced costs" (38% and 40%) and having "a non-judgmental/non-stigmatizing approach/atmosphere" (37% and 39%). These percentages were even higher among people who inject drugs and people living with HIV. The great majority of participants (91%) also expressed a strong preference for having testing and treatment in the same place for "convenience" (34%) and "continuation of follow-up from testing to treatment" (33%).

Peer-driven semi-structured interviews or focus group discussions (International Network of People Who Use Drugs (INPUD)) (Web Annex D)

Across four key populations (gay and bisexual men, male and female sex workers, people who inject drugs and transgender people), 230 individuals in 68 countries participated in either a semi-structured interview (SSI) or a focus group discussion (FGD) on the themes of decentralization, integration, the role of peer workers, stigma and discrimination. There were several key findings:

- Across all four key populations, there was a universal preference for community-based services for HIV, STIs and HCV. Participants described community-led services as critical to promoting the health and human rights of marginalized groups and a counter-balance to stigmatizing health care settings. The main advantages of community-led services highlighted were: the greater accessibility of services; specific understanding of community health needs and comprehensive approach to key populations' well-being; provision of safe spaces for communities to gather, organize and advocate; and more effective communication with communities in ways that are credible, relevant, nonjudgmental, trustworthy and accessible. Effective community-led service models mentioned by participants included drop-in centres, mobile clinics, peer outreach and one-stop shops.

- Participants expressed strong support for offering HCV testing and DAA treatment in a wide range of settings, including at harm reduction services (NSPs, OAMT clinics, drop-in centres), as well as in general practice and hospital settings, to maximize access and reduce barriers, but also at the same site ("one-stop shops") to reduce loss to follow-up.
- Participants emphasized the importance of offering HCV DAA treatment alongside HCV prevention for people in prisons, where access to harm reduction measures is often completely lacking.

Multi-country rapid qualitative assessment (FIND) (Web Annex D)

A survey was undertaken in 2020 among potential end users of HCV services and health care workers to understand their values and preferences concerning hepatitis C self-testing (HCVST) and perspectives on current hepatitis C testing services. Across 10 countries, populations included were: general population and health care workers (in Rwanda, Thailand and Ukraine); men who have sex with men (in Brazil, India and the Philippines), people who use drugs/people who inject drugs (in Costa Rica, India, Indonesia, Kyrgyzstan and South Africa. Among respondents, 460 participated in individual interviews; 220, in group interviews; and 257, in Participatory Action Research. The original analyses were re-reviewed in 2021 to synthesize relevant data on values and preferences relating to decentralization, integration and task sharing of HCV testing and treatment services. Key observations were: Existing HCV services were described as inconvenient, with complex processes, long queues, requirement for immediate payment and lack of information on how to access tests and treatments. Simplification of processes through decentralization and integration with primary care and harm reduction services, especially the "one-stop shop" for same-day testing and treatment, was strongly supported. But there were concerns about the potential for increasing stigma if such HCV test-and-treat services were offered only to vulnerable and already stigmatized populations. Partial decentralization, where only testing is done at a community level, was judged an ineffective approach if prompt access to treatment could not be guaranteed.

5.4.4 Equity

The systematic review showed that the impact of full decentralization/integration of HCV testing and treatment has been greatest among people who inject drugs and prisoners – two key populations that have major difficulties in getting tested, linked to care and navigating tertiary care facilities for treatment, with high rates of loss to follow-up *(154-156)*. The Guideline Development Group, therefore, concluded that providing HCV testing and treatment at lower-level facilities integrated with existing harm reduction services would increase equity, as benefits of co-location of services for patient care were greatest among marginalized populations who currently have major difficulties accessing health services.

5.4.5 Feasibility

Compared with HIV care, there are even greater opportunities for decentralization of HCV care to lower-level facilities *(139)*. The simplicity of short-course, curative, pangenotypic DAA regimens with minimal side-effects means that care and treatment require minimal expertise and monitoring. There are now multiple examples of successful models of decentralized viral hepatitis testing and treatment services emerging in high-burden countries, both in primary care for the general population and at harm reduction sites for people who inject drugs *(157)*. We highlight below country case studies of decentralized and integrated HCV care models in primary care in Cambodia, Malaysia and Georgia and, from Médecins du Monde, multi-country peer-based HCV screening and treatment for people who inject drugs integrated into a harm reduction model in Georgia, Kenya, Viet Nam and Myanmar (Boxes 6.1, 6.2, 6.3 and 6.4 – Case studies).

5.5 Implementation considerations

Implementation of the recommendations should be informed by local context, including HCV epidemiology and the prevalence of other comorbidities, the availability of resources, the organization and capacity of the health system and anticipated cost–effectiveness.

- **Decentralization and/or integration of HCV testing and treatment services** will require additional training and supervision for health care workers (see Task-sharing implementation considerations, section 6.6), access to quality-assured RDTs or collection and analysis of blood specimens, good specimen referral networks and documentation of results, including other features such as enhanced connectivity for return of results and an electronic results system. Planning and coordination are also important for delivery of integrated care, including establishment of integrated data systems and consistent cross-training of health care providers.
- **Implementation alongside other existing good practice principles of simplified service delivery** (see Box 5.1). These include comprehensive national planning, simple and standardized algorithms, differentiated care strategy, community engagement and peer support, strategies for more efficient procurement and supply management, and data systems to monitor the quality of individual care and coverage.
- **Adaptation of service delivery recommendations for different contexts and high-income countries:** Decentralization and integration require understanding of context, needs, service gaps and overall costs and benefits and the programmatic data to inform decision-making.
    - Decentralization of HCV testing and treatment services and/or integration into existing health services may not be appropriate for all settings or acceptable to all clients, and the relative benefits should be assessed according to the context. For example, decentralization of services may be inefficient and costly in high-income countries with a low burden of HCV infection, and a centralized service delivery model with community linkage may be more appropriate.

- The selection of facilities for decentralization should take into consideration geographic distribution of the most affected populations, and will not be applicable to all primary health care facilities.
- Where care is partially decentralized, ie. testing at a community site and treatment at a different hospital site, it should be accompanied by efforts to strengthen linkage and referral systems. Community-based treatment programmes should be linked with care at health facilities and with adequate laboratory, diagnostics, monitoring and evaluation and drug and supply management systems. Mobile outreach services may also be utilized to address hot spots, which can be identified via routine HCV testing.

  Adaptations may be needed for specific populations. Although hepatitis care and treatment services for key populations can be provided in decentralized settings, it should be recognized that not all health care centres are equipped equally to deal with the specialized needs of people who use drugs. The experience of stigma and discrimination is one of the major problems in accessing services for people who inject drugs, and this problem may be greater at some facilities than others. Some may choose to receive their hepatitis care in a facility that is not close to their homes because of concerns about stigma and disclosure.

5.6 Research gaps

- There is a need for more methodologically rigorous studies comparing packages of different service delivery interventions, focussing on different steps in the care cascade. Such studies should assess how well these interventions promote the uptake of HCV testing, linkage to assessment and uptake of treatment, especially in LMICs. Studies should provide a full description of the service delivery model, and evaluation should capture the effectiveness of interventions across the entire continuum of care and not only the treatment-related outcomes.
- Implementation research is especially needed on different models of fully decentralized and integrated HCV testing, care and treatment for the general population in primary care settings, and models of peer supported service delivery.
- Costing and cost–effectiveness data for different decentralized and integrated models of care should be collected, to allow for comparative analyses.
- Examination is needed of various strategies to promote testing and treatment access in LMICs, such as mobile outreach services, especially for homeless populations; pharmacy-led testing and treatment initiation; and Internet-based linkage programmes. Mobile outreach services may also be utilized to target hot spots, identified through routine HCV testing.

SIMPLIFIED SERVICE DELIVERY

CHAPTER 6. TASK SHARING

6.1 Recommendation: task sharing[1]

New recommendation

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)

6.2 Background

Until recently, delivery of viral hepatitis testing and treatment in many countries relied on specialist-led (usually by a hepatologist or gastroenterologist) and centralized care models in hospital settings to administer complex treatment *(120, 121)*. However, many countries affected by HCV infection face shortages of trained health workers and specialists in the management of viral hepatitis. The availability now of short-course oral, curative pangenotypic HCV DAA treatment regimens with few if any side-effects requires minimal expertise and monitoring and has the potential to be safely provided by non-specialists, including primary care physicians and nurses at peripheral or community facilities *(158)*.

Task sharing to non-specialists is a pragmatic response to shortages of the health workforce to support decentralized care. It was strongly recommended in 2014 by WHO for HIV care, based on a comprehensive evidence base, and has been widely adopted to expand access to testing and ART initiation and follow-up globally *(143, 159)*. In 2016 WHO also strongly recommended that lay providers who are trained and supervised be able to independently conduct HIV testing RTCs, and nurses, to initiate ART. Effective task sharing for ART delivery by non-specialists or nurses requires appropriate training at the decentralized site and access to additional support or referral to tertiary or specialist sites for complex cases *(123, 160, 161)*. There is now a substantial evidence base on task sharing HCV care to non-specialist health care workers to inform updated WHO recommendations.

[1] Task sharing refers to the rational redistribution of tasks from "higher-level" cadres of health care providers to other cadres, such as trained lay providers, including community members.

6.3 Summary of the evidence (Web Annex C)

A systematic review and meta-analysis of 142 studies from 33 countries (20 (14%) from LMICs) examined the effectiveness of key simplified service delivery interventions (decentralization, integration and task sharing to non-specialists) on outcomes across the HCV cascade of care (uptake of HCV serologic testing, NAT, treatment, cure assessment and SVR12 (cure). There were 46 (30%) studies with care delivered by non-specialists, 24 (16%) delivered by non-specialists supported through telehealth and 51 (33%) with care delivered by specialists. Of the 142 studies, 80 (56%) were among people who inject drugs, 20 (14%) among people in prisons, five (4%) in people living with HIV and 37 (26%) in the general population. Some 123 studies (87%) were single-arm observational studies, and 11 (8%) were comparator observational studies. There were only six randomized controlled trials.

Across all populations, task sharing of care and treatment with DAA-based regimens to a non-specialist (primary care physician, addiction specialist or nurse) was associated with consistently high SVR12 cure rates, similar to those with treatment delivered by specialists, across all populations and settings. This included among people who inject drugs (non-specialist 96% [95% CI 93–98] versus specialist 92% [88–96]), people in prisons (non-specialist 98% [96–99] versus specialist 100% [77–100]), people living with HIV (non-specialist 98% [96–99] versus specialist 100% [96–100]) and the general population (non-specialist 94% [90–97] versus specialist 94% [92–96]). Of note, task sharing of care and treatment was associated with similar SVR12 cure rates even when using the more complex interferon-based regimens. In an analysis of the five studies that had direct within-study comparisons of task sharing to non-specialists versus no task sharing, SVR12 rates with DAA regimens were high for all populations analysed. Results were also consistent between the comparator and non-comparator studies (Table 6.1).

The key limitations of the review were that it was based largely on single-arm observational studies, but there were five studies that had a comparator arm of specialist versus non-specialist care, and results were consistent between comparator and non-comparator studies. There was also an under-representation of studies from LMICs, and there were insufficient data to examine the impact of task sharing on uptake of testing and treatment.

TABLE 6.1. Comparison of SVR12 outcomes with DAA treatment regimens in studies with or without comparator groups, according to population and level of decentralization

	Non-specialist care, SVR12 % (95% CI)	Specialist care, SVR12 % (95% CI)	p value
People who inject drugs			
Comparator studies	93% (86–98)	95% (92–97)	0.460
Wade et al. *(2018)*, RCT	PCPs or nurses 100% (76–100)	100% (74–100)	..
McClure et al. *(2017)*, PCS	Nurses 88% (78–95); GPs 93% (82–99)	93% (90–95)	..
Non-comparator studies	96% (94–98) (n=22 studies)	92% (86–96) (n=8 studies)	0.145
General population			
Comparator studies	95% (92–98)	94% (91–96)	0.466
Cooper et al *(2017)*, RCS	Nurses 95% (74–100)	95% (91–97)	
Kattakuzhy et al. *(2017)*, NRS	PCPs 95% (90–98); nurses 95% (90–98)	92% (89–95)	..
Non-comparator studies	93% (87–97) (n=5 studies)	94% (91–97) (n=9 studies)	0.737
People living with HIV			
Comparator studies	94% (88–98)	100% (93–100)	0.065
Doyle et al. *(2018)*, NRS	Nurses 94% (88–98)	100% (93–100)	..
Non-comparator studies	99% (97–100) (n=3 studies)	NA	NA

NRS = non-randomized study; PCP: primary care physician; PCS = prospective cohort study; RCT = randomized controlled trial;

6.3.1 Additional supporting evidence from the HIV literature

Multiple systematic reviews from different areas of health care support the general conclusion that good health outcomes can be achieved by devolving tasks to nurses and lay or community health workers with appropriate training and supervision *(4, 162, 163)*. Task sharing has been adopted for around two decades to expand HIV testing and treatment across the globe, especially in resource-limited settings where there is a shortage of health care professionals *(164, 165)*. WHO already recommends that lay providers who are trained and supervised can independently perform HIV counselling and testing using RDTs and that nurses can provide HIV testing in pregnancy and, now, initiate ART *(166, 167)*. The public health benefits of lay providers distributing ART have also resulted in an overall increase in the number of providers to overcome the shortage of facility personnel, reduced clinic congestion and provided services closer to communities, which supports long-term retention in care *(8)*.

6.4 Rationale for the recommendations

6.4.1 Balance of benefits and harms

The Guideline Development Group made a strong recommendation for adoption of task sharing to non-specialists, including primary care physicians and nurses, based on moderate certainty of evidence of comparable cure rates between specialists and non-specialists across all populations and in all settings. Task sharing is a key intervention to improve access to HCV diagnosis and treatment, especially among people who inject drugs and people in prisons, who are more challenging populations to reach and treat. There is limited evidence of reported harms with task sharing in HCV service delivery, but adequate training and support is required to ensure referral for more complex cases *(139)*. It is not yet understood how task sharing for hepatitis C care and treatment could apply for children, due to the need to adjust the dosage for younger children.

Task sharing is a key intervention to improve access to HCV diagnosis and treatment, especially among people who inject drugs and people in prisons.

6.4.2 Values and preferences and acceptability (Web Annex D)

Given the considerable potential benefits and minimal harms, the Guidelines Development Group considered that the recommendation was not sensitive to variability in preferences/values regarding outcomes. Three related surveys or series of in-depth interviews were undertaken among different populations affected by HCV to inform an understanding of the values, preferences and acceptability of task sharing of HCV services to non-specialists. In all three surveys, regardless of support for or against task sharing of HCV testing and treatment to community-based health care workers, there was unanimous support for the importance of a non-judgmental/non-stigmatizing approach among health care providers and the need to sensitize and train primary care physicians and other health care workers. However, the majority of respondents thought that task sharing would not increase people's access to testing and treatment unless health care workers' attitudes improved.

Across the three different surveys, there were diverse perspectives on the issues of task sharing of HCV testing and treatment to non-specialists. Respondents recognized that non-specialists (primary care physicians, nurses, community health workers, pharmacists) are already engaged and play important roles in HCV testing and treatment. While many respondents thought that testing uptake and linkage-to-care would increase if people were able to receive HCV care from their trusted regular care provider, others, particularly from marginalized groups, such as people who inject drugs, thought this approach would be a deterrent to seeking care due to the perceived judgemental attitudes of health care workers.

Although participants of the World Hepatitis Alliance survey showed a strong preference for testing and treatment in community-based settings outside of conventional health care settings such as hospitals or general practitioner's clinics, they also showed a preference for seeing specialists when discussing health needs related to hepatitis C. In response to the question, "With whom would you prefer to discuss your health needs related to hepatitis C?" (n=166), "specialist doctor" was the most popular choice (48%), followed by "community-friendly medical personnel" (23%), but only 10% indicated "general practitioner" (11%) or "community/peer worker" (10%). The subgroup of current or former people who inject drugs showed a greater preference for "community/peer workers" and reluctance to discuss their HCV care with a "general practitioner". The survey concluded that providing a mix of culturally competent services delivered by specialist and non-specialist community-friendly medical personnel was valued, and that this would satisfy the preferences of most participants.

The INPUD peer-driven semi-structured interviews (SSI) or focus group discussions (FGD) highlighted the almost universal experience among people who use drugs of stigma and discrimination from health care workers, and the need to sensitize and train primary care physicians and other health care workers. Across regions, peer workers and peer-based services were highly valued, especially by members of key populations, due to their capacity to engage and gain trust. There was strong support for additional peer-based and community-led HIV/STI/HCV services.

6.4.3 Resource considerations and access issues

Four studies have evaluated the cost–effectiveness of different levels of decentralization and task sharing *(150-153)*. The simplified care models with task sharing to nurses or non-specialist doctors resulted in lower costs and either similar or better outcomes and were considered very cost–effective.

6.4.4 Feasibility

Many studies show the feasibility of task sharing of HCV diagnosis and treatment to non-specialists in primary care and among the marginalized and hard-to-reach people who inject drugs at OAMT and NSP sites *(139)*.

6.5 Implementation considerations

- **Defining roles and standards of care:** Standards of care should be defined for different levels of the health system, including the private sector. The role of each cadre of health worker should match their skills and capacity, and the lines of responsibility should be clear and well understood. For example, health care staff at a decentralized facility should be able to identify signs and symptoms of advanced liver disease or interpretation of test (such as APRI or FIB-4) for the appropriate referral of persons in need of a higher level of care, especially among older patients. There is a need to ensure an appropriate mix of health care workers at peripheral facilities.

- **Training and mentorship:** Effective task sharing with non-specialist doctors or nurses requires provision of appropriate training and ongoing mentorship at the decentralized site and access to additional support or referral to tertiary or specialist sites for more complex cases *(148)* 168). This should include awareness-raising and training to provide non-stigmatizing, non-discriminatory health care to key populations.
- **Regulatory framework:** An appropriate regulatory framework (legislation, regulations, policies and guidelines) is needed to enable tasks to be performed by different cadres of health care workers. In some countries task sharing and delegation may require changes to legislation and rules and procedures *(160)*.
- The updated *Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations* now include an additional recommendation for peer navigators to support people from key populations to start HIV, viral hepatitis or STI treatment to remain in care.

BOX 6.1 Case study: CAMBODIA – Médecins Sans Frontières (MSF) – simplified model of decentralized HCV care in a rural health operational district in Battambang province, Cambodia *(169-171)*

In LMICs, increasing overall access to HCV care remains an ongoing issue, particularly for populations outside of urban centres. MSF implemented a simplified model of decentralized HCV care in a rural health operational district in Battambang province, Cambodia.

Model of care

The pilot project was implemented from June 2020 among the adult residents (≥18 years of age) of two operational districts (ODs) in Battambang province with 27 participating rural health centres. Voluntary HCV antibody screening was undertaken through both active case finding (testing people in villages) and passive case finding (patients presenting to rural health centres). Serology testing was done with an RDT (SD Bioline®). If HCV-Ab serology positive, testing for HIV via rapid test, blood glucose, and blood pressure were also offered. Blood draw for HCV viral load (HCV-VL) test was done weekly at each health centre due to cold chain considerations for HCV viral load testing at the district referral hospital lab, using GeneXpert – a near POC molecular technology. Health center staff (primarily nurses) were trained in and assessed for competency to identify signs of decompensated liver cirrhosis and provided two-day training in the nurse-led initiation model. To expedite DAA initiation for HCV viraemic patients, pre-treatment assessment was performed by nurses. Viraemic patients who did not have additional complications received all HCV care follow-up with trained nurses at the local health centres. Patients who had decompensated cirrhosis or previous treatment with DAA regimens, HBV co-infection or other comorbidities requiring

observation continued receiving care under a general physician at the local referral hospital. Patients eligible for treatment were prescribed oral sofosbuvir (400 mg) and daclatasvir (60 mg) once a day for 12 weeks, or 24 weeks for patients with decompensated cirrhosis and those with prior DAA treatment.

Findings

Between 1st June 2020 and the 30th September 2020, 10,960 residents were screened - 4,736 (43%) by active case finding and 6,224 (57%) by passive case finding. This represent around 8% of the estimated 136 571 adults in the health operational district of Moung Russei. Of the 920 HCV-Ab positive, 903 (98%) had a HCV RNA viral load testing, 547 (61%) were HCV viraemic (median age was 58 years). Among the 547 viraemic patients, linkage to treatment and follow-up care was high, overall 97% were initiated onto DAA treatment and 204 patients (38%) were referred for DAA initiation at the patient's relevant referral hospital. Of 547 patients diagnosed as HCV-VL positive, 97% initiated onto DAA treatment. 204 patients (38%) were referred for DAA initiation at the patient's relevant referral hospital. 329 patients (62%) were initiated onto DAA treatment at a health centre, and median turn-around time between HCV-VL testing date and initiation appointment at the health center was 8 days. All 329 patients (100%) initiating DAAs at the health centre completed treatment; 315 (96%) returned for 12-week post-treatment testing, among whom, and 310 (98.4%) achieved SVR12 with five treatment failures.

Conclusion

The pilot project and nurse-led initiation (NLI) care model showed that a highly simplified, decentralized model of HCV care with task-sharing to nurses can be integrated with a rural public health system in a low-income country while maintaining high patient retention, treatment efficacy and safety. The project delivered care via accessible, decentralized primary health centres using non-specialist clinical staff, thereby enhancing the efficient use of limited resources and maximizing the potential to test and treat individuals living with HCV infection.

BOX 6.2 Case study: MALAYSIA – Ministry of Health – implementation of decentralized and integrated care and task sharing in Malaysia: Operational/implementation issues in national scale-up *(172)*

Malaysia is an upper-middle-income country with a low HCV burden and prevalence of around 0.3%.

The initial success of the Malaysian HCV programme, with progressive decentralization of HCV screening and treatment, is attributed to a multi-pronged strategy, defined by:

Government commitment and leadership

- The Ministry of Health in Malaysia committed to a goal of HCV elimination with goals to diagnose 90% of HCV-infected persons and treat 80% of those eligible.
- A 5-year national strategic plan was launched in 2019, with a plan for HCV treatment scale-up based on decentralized and integrated care.
- A series of clinical practice guidelines on HCV management also launched in 2019, providing evidence-based recommendations and simplified algorithms for HCV care.

Improved access to DAAs

- Malaysia issued a compulsory license for sofosbuvir in September 2017, which resulted in availability of the sofosbuvir/daclatasvir regimen at less than US$ 300 per client in public health facilities across the country.
- The Ministry of Health organized distribution of DAAs across public health facilities in the country through centralized coordination and pooled procurement.

Model of care: progressive decentralization in HCV care delivery

- A progressive shift in the HCV care model from a hospital-based to a community-based model. The decentralization of HCV screening and treatment was first piloted in 25 primary health care (PHC) centres through the HEAD-Start Project and subsequently extended to another 287 PHC centres.
- The capacity building of health care workers was undertaken through a series of training sessions (in person and online), led by the Gastroenterology and Hepatology Services Committee and Public Health Division of the Ministry of Health.
- HCV Programme Implementation Review Workshops were also organized periodically, involving family medicine physicians, general medical officers, allied health professionals and officers from correctional settings and civil society organizations (CSOs) to discuss clinical management and service delivery issues related to HCV care and discuss possible solutions.

Conclusions

Following progressive simplification and decentralization of HCV care in the country, as of August 2021, 11 000 HCV patients had been treated with DAAs, despite the impact of the COVID-19 pandemic on health services.

BOX 6.3 Case study: GEORGIA – On the path to HCV elimination – lessons from Georgia *(173)*

Georgia established the world's first national hepatitis C elimination program in 2015. By October 2021, 2.3 million people had been screened, and of the 150 000 estimated to have chronic hepatitis C virus (HCV) infection, 95 000 have been identified and 76 000 treated. This has been achieved through continuous improvements and simplification in the HCV testing and treatment pathway to overcome key barriers to screening, linkage-to-care and treatment and to decentralize care to primary and non-specialized care sites.

Expansion of screening

The diagnostic strategy evolved from an initial focus on testing and treatment of people with advanced liver disease to an expanded hospital screening program in November 2016 with the offer of rapid antibody testing to all admitted patients. This led to a threefold increase in screening uptake in the first six months: 14 623 unique persons had screened per month in May–October, 2016 versus 46 648 per month in November 2016–April 2017 *(173)*. In 2018 primary care centres in one region piloted an integrated HCV/HIV/TB testing project, in which all people presenting to the facility were offered screening for all three infections; the project demonstrated a 60% increase in screening coverage in the pilot region *(174)*. By the end of 2020, the integrated testing approach had expanded to 1044 primary care sites nationally, which conducted 636 401 screening tests (31% of total HCV screening tests performed in the country during the same time period) and identified 5185 HCV-positive persons (16.2% of all identified countrywide).

Simplification of diagnostic pathways

Ensuring high-quality and diversified diagnostic capacity has been one of the important directions of the elimination strategy. Following WHO recommendations, RDTs or laboratory-based immunoassays are offered as a screening tool at 1361 locations countrywide. Initially, when patients screened antibody-positive, they had to independently seek viremia testing at specialized HCV provider clinics. As a result, only 19.8% of HCV antibody-positive persons had a viral load test *(173)*. In 2017 reflex testing was introduced, in which HCV antibody-positive specimens are automatically reflexed to HCV RNA or core Ag testing, or a new blood sample is drawn for confirmation immediately after a reactive antibody test result. As a result, the proportion of people tested for viremia in hospital screening programmes increased dramatically, to 79.5%. Confirmatory testing significantly diversified over time and is now available in more than 40 sites, with several platforms available for different models of service delivery. In 2017–2018 HCVcAg and GeneXpert HCV viral load testing were introduced, and by 2020 these two testing methods accounted for 50.4% of all viremia testing in the country.

Decentralization and integration with existing primary care and harm reduction services

Georgia's elimination program has continuously evolved toward people-centred health care delivery through integration and decentralization of HCV testing and, now, decentralization of treatment to primary care and harm reduction sites. In 2018 a "one stop shop" approach was piloted in four primary care centres, and 81.4% of people identified there to have chronic HCV infection initiated treatment, with cure rates reaching 99.1% *(175)*. The model became part of standard service delivery, expanding to 10 locations countrywide by the end of 2019; further expansion was planned but limited by the COVID-19 pandemic. At the same time, integration of care with harm reduction services has led to significant increases in screening rates among persons who inject drugs, from 3638 tests per year during 2006–2014 to 21 551 tests per year after 2015 *(176)*. HCV screening has been integrated with NSP at 16 fixed sites and nine mobile units. Of those, four NSP sites offer viremia testing with GeneXpert and treatment. An additional 21 OAMT clinics offer screening services for HCV. Engagement in the care continuum among clients of NSPs and OAMTs showed viremia testing uptake ranging between 80% and 86%, treatment initiation of 85–87% among those diagnosed with chronic HCV infection (with faster initiation among those accessing integrated services) and cure rates of 98% *(177, 178)*. Successful service decentralization and integration have been possible through simplified diagnostic and treatment algorithms. Complex treatment selection and monitoring algorithms have been gradually simplified as the programme switched to all-oral pangenotypic DAA regimens, with concomitant increased cure rates from 82.1% to 98.9% *(179)*.

Task sharing

Initially, only infectious disease specialists could treat HCV. By early 2016 other specialists (for example, gastroenterologists) were able to provide care. The programme has adopted further task sharing by allowing primary care physicians to treat patients and, thus, supporting decentralization of HCV testing and treatment as part of the package of services delivered at primary health care and harm reduction.

BOX 6.4 Case study: GEORGIA, KENYA, VIET NAM and MYANMAR – Médecins du monde

In Georgia, Kenya and Viet Nam, a series of demonstration projects with peer-based HCV screening and treatment have been integrated into harm reduction services, specifically with peer navigation as the foundation of initiating and guiding the clients through the cascade of care.

Georgia has a high prevalence of hepatitis C virus infection, and it is estimated that injecting drug use accounts for up to one quarter of infections. The harm reduction programme of Médecins du Monde (MdM) integrated a proactive peer-based care model, including awareness raising, free screening for viral hepatitis and HIV and Fibroscan for staging of liver disease, into a community site for people who inject drugs. Using a specifically designed case-management model, peer navigators pro-actively guided people who inject drugs through different steps of the treatment pathway, including initial medical assessments, during treatment and post-treatment. Excellent uptake, adherence and retention were achieved across the cascade of care – around 90% missed none of the fortnightly medical appointments, and 98% completed treatment. Follow-up data 15 months after the end of treatment demonstrated low rates of reinfection (incidence of 1.2 per 100 patient-years). Based on these experiences and in collaboration with the health authorities, this model is now being rolled out on a national scale. Several harm reduction sites have further improved on this model, and now provide confirmatory (GeneXpert®) testing and treatment directly in the harm reduction centres, as part of a "one-stop shop" service *(180)*.

The Kenyan and Viet Nam experiences have demonstrated the feasibility of reproducing this model in two very different contexts. In a collaboration between Médecins Sans Frontières (MSF) and MdM, HCV treatment services have been integrated within MdM's existing harm reduction programmes in Nairobi as a "one-stop shop" *(181, 182)*. Key features of these projects have been the strong outreach-based approach, providing delivery of treatment at outreach sites on a case-by-case basis. The Viet Nam experience also showed that this model can "plug into" a medium/low-level public health facility and achieve a form of task sharing, with care delivered by an experienced HIV district hospital team without the involvement of a specialist hepatologist. This collaboration between a district-level hospital and a peer-support network enabled 97% of patients to be retained in care during treatment, with a 98% cure rate for those who completed treatment *(183)*.

Integrating HCV treatment component into an established HIV treatment programme – Myanmar

Myanmar is the world's second biggest producer of opium, and drug use is extremely widespread. MdM has been providing comprehensive harm reduction services among people who inject drugs in Kachin State since 1994, addressing the HIV epidemic among people who inject drugs. The programme reaches up to 7000 people who use drugs with a package of HIV prevention and treatment services, including through three HIV clinics providing ART for around 2500 people who inject drugs.

In 2019, MdM, with support from Médecins Sans Frontières (MSF), added an HCV treatment programme in three HIV clinics. The whole harm reduction (HIV-focused) intervention model was maintained, simply adding an HCV cascade. Peer navigators were trained to include an awareness session on hepatitis, HCV rapid testing was introduced alongside HIV screening, a GeneXpert® instrument was added to one of the clinic laboratories, and pangenotypic sofosbuvir/daclatasvir treatment was made available. A programme manager and additional counsellors were recruited, as well as another medical doctor to support all the clinics as needed. Peer navigation for adherence and follow-up were included as part of the existing HIV model.

With minimal additional resources, HCV testing and treatment has become an effective, fully integrated part of an HIV-oriented harm reduction project. Despite the remote populations and extreme complex humanitarian context, cure rates exceed 86% and within two years the programme had already treated the majority of eligible patients.

6.6 Existing 2018 additional good practice principles for simplified service delivery *(1)*

6.6.1 National planning for HCV elimination

In 2015 WHO published a manual to guide national programme managers in developing or strengthening national viral hepatitis plans *(184)*. The manual is aligned with a health systems approach to disease planning and supports an evidence-based decision-making process. It includes a template for a national hepatitis plan that covers prevention, testing and treatment within the framework of universal health coverage principles and other planning tools. National stakeholders should also use the plan to agree on the service coverage targets for the interventions necessary to achieve elimination.

6.6.2 Simple standardized algorithms

A simplified algorithm for testing, treatment and monitoring with five key steps that can be adapted for use at the national level has now been updated (see Figure 1). The three updated steps are: alternative option of an HCV point-of-care RNA assay for diagnosis of HCV viraemic infection and as a test of cure; the offer of pan-genotypic treatment to now all adolescents and children ≥3 years, in addition to adults; and assessment and management of treatment failure.

6.6.3 Differentiated HCV care and treatment

Currently, the majority of HCV care and treatment during this early phase of scale up is facility- based, and not differentiated according to individual needs. Differentiated care is defined as a client-centred approach that simplifies and adapts services across the cascade, in ways that both serve the needs better of those with more complex problems requiring prompt or specialized clinical care but also relieves overburdened hepatitis clinics in central hospitals. Based on an evidence-based differentiated care framework recommended by WHO and widely adopted in HIV treatment and care programmes *(166)*, a similar approach has been adopted to support decentralized management of HCV infection.

Broadly, three groups of HCV-infected persons with specific needs can be identified. Table 6.2 summarizes these three groups, their anticipated care needs, the most appropriate setting to deliver care and the type of provider needed. The majority of persons with HCV will have early-stage liver disease and can be treated at facility level or potentially even in the community. Only a small proportion will require more intensive clinical or psychosocial support. However, this will vary considerably according to the epidemic profile of the country, and the maturity of the treatment response and diagnosis rate.

1. **Persons clinically well and stable:** This represents the majority of persons diagnosed, and includes those with no evidence of cirrhosis, serious comorbidities, mental health issues or active drug use; and the ability to comprehend issues of adherence and prevention messages.
2. **Persons requiring more intensive clinical support:** This includes persons presenting to care with advanced liver disease or serious clinical or psychological comorbidities, previous treatment failure that requires either a more intensive or fast-tracked clinical and care package to manage life-threatening clinical problems and in order to initiate treatment with more intensive monitoring.
3. **Persons requiring more intensive psychosocial/mental health support, or intercultural or language support:** This may include those with mental health issues, people who inject drugs, those with alcohol misuse, or adolescents requiring additional support and counselling. Migrant populations and indigenous peoples may also require more intensive intercultural or language support.

TABLE 6.2 Potential differentiated care needs and approaches to 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 (for example, 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

6.6.4 HCV testing, care and treatment integrated with existing services

The goal of programme collaboration is to create integrated delivery systems that can facilitate access to hepatitis testing, treatment and other health services. There are three types of potential service integration:

1. providing testing for HCV infection in different settings (for example, in HIV/ART, TB, STI, non-communicable disease screening or antenatal clinics);
2. integrating the diagnosis of hepatitis with diagnostic platforms and laboratory services used for other infections;
3. integrated service delivery of care, prevention and treatment (for example, HCV care at harm reduction or HIV sites).

Increased access and rapid scale up of HCV treatment and care will require a significant change in the way that services are delivered. Where possible, HCV services (testing and DAA treatment) can integrate the public health system. In many cases, this integration goes down to primary health care facilities. It makes use of existing HIV and harm reduction services (OAMT and/or needle exchange programmes) or prison health services to increase access, especially for people who inject drugs. Existing WHO guidance on delivery of effective OAMT programmes is available *(8)*. Continuity of prevention and care is needed to ensure ongoing harm reduction measures and avoid reinfection, especially among people who inject drugs and men who have sex with men. Integration of services means not only provision of related services at a single setting, but also linking reporting systems to share information between settings and providers.

6.6.5 Providing testing for HCV infection in different settings

WHO already recommends integration of HIV testing into a range of other clinical services, such as services for TB, HIV/ART, maternal and child health, sexual and reproductive health (STI clinics), mental health and harm reduction programmes, migrant and refugee services, and in prisons *(2)*. Integrating HCV and HIV testing will be particularly important in populations with high-risk behaviours for both infections, such as people who inject drugs, men who have sex with men and incarcerated persons who have a high prevalence of both HIV and HCV infection.

The primary purpose of integration is to make HBV, HCV and HIV testing more convenient for people coming to health facilities, and so expand the reach and uptake of viral hepatitis testing. For the HCV-infected person, integration of hepatitis testing into other health services may facilitate addressing other health needs at the same time, thereby saving time and money. For the health system, integration may reduce duplication of services and improve coordination (for example, in stock management of diagnostic assays).

6.6.6 Integrating the diagnosis of viral hepatitis C with diagnostic platforms and laboratory services used for other infections

Combination integrated multidisease serological tests

The use of combination integrated fingerstick whole blood- or oral-based multidisease assays allow for integrated testing of HIV, HBV and HCV. Using a single specimen improves the efficiency of testing programmes, especially in populations with a high prevalence of HIV/HCV or HBV/HCV coinfection. While not widely approved or available, preliminary independent evaluation of these combination RDT assays appear promising *(185)*.

Shared use of HIV or TB multidisease platforms for HCV RNA testing

The introduction of multidisease testing devices or analyzers (also known as polyvalent testing platforms) brings new opportunities for collaboration and integration, and can both increase access as well as provide significant system efficiencies, with cost-savings. Countries with existing multidisease platforms for HIV viral load, HIV infant diagnosis or TB diagnosis and drug resistance testing, or those that are planning for their introduction can consider collaboration and integration of HCV viral load testing *(186)*. This includes both high-throughput laboratory-based instruments for HIV viral load and HIV infant diagnosis, SARS-CoV-2 and point-of-care NAT instruments such as GeneXpert for HIV and TB.

6.6.7 Community engagement and peer support, including addressing stigma and discrimination in the general population Updated

Peer-led interventions have been effective in increasing access, care and treatment, and supporting adherence to treatment, for both hepatitis and other infectious diseases particularly for marginalized population groups such as people who inject drugs *(4, 7, 146)*. In addition to providing services, peers can act as role models and offer non-judgemental support that may contribute to reducing stigma and improving the acceptability of services.

6.6.8 Strategies for more efficient procurement and supply management of medicines and diagnostics

Access to DAAs for hepatitis C has improved since their initial registration in 2013 *(55)*. In 2017 62% of those infected with HCV lived in countries where generic medicines could be procured. Countries that made use of this possibility and registered multiple medicines from different manufacturers managed to achieve a major reduction in prices *(187)*. However, initial progress in access to pan genotypic DAAs has been mostly for sofosbuvir/daclatasvir combinations (Table 4.1).

Key steps to increase the availability of DAA and in vitro diagnostics (IVDs) at country level include the following *(9)*:

1. **Selecting products:** formulating national testing and treatment guidelines that specify which brands of medicines and IVDs diagnostic assays should be used. WHO- prequalified products are listed at: https://extranet.who.int/pqweb/vitro-diagnostics/prequalification-reports/whopr, and also http://www.who.int/diagnostics_laboratory/ evaluations/PQ_list/en/. See also https://extranet.who.int/pqweb/medicines/prequalification-reports

2. **Determining whether generic medicines are available in the country:** If DAAs are not protected by a patent or if the country is included in the respective license agreement, procurement of generic medicines from various sources is possible. Otherwise, the country needs to enter into price negotiations with the originator company or through regional associations of countries. If this does not yield satisfactory results, use the flexibilities contained in the World Trade Organization (WTO) Agreement on Trade Related Intellectual Property Rights *(9)*.

3. **Registration and inclusion in the national essential medicines list:** DAAs need to be registered with the national regulatory authority and included in the national essential medicines list. If access to generic medicines is possible, registration of products from as many manufacturers as possible will increase competition and lower prices.

4. **Quantification and forecasting of demand for commodities:** To estimate the volume of products required to meet programme demand, managers need to estimate the size of the infected population in need of treatment and the expected rate of scale up for testing and treatment activities.

5. **Procurement of commodities:** Procurement mechanisms can include (i) a competitive tendering process in case of registration of multiple manufacturers of generic medicines or (ii) price/volume negotiation with the originators if generic medicines cannot be procured. A pooled procurement mechanism (for example, the Strategic Fund of the Pan American Health Organization) is another option for economies of scale in procurement of commodities, including diagnostics.

6.6.9 Data systems for monitoring the quality and cascade of care

WHO has developed a monitoring and evaluation framework to enable Member States to report on hepatitis elimination *(188)*. Three indicators address the cascade of care, including the proportion of infected persons diagnosed (core indicator C6b), treatment initiation rate (core indicator C7b) and the proportion of those treated who are cured (C8b). In an initial assessment phase, triangulation of data from different sources may be used to generate an initial estimate of the three core indicators of the cascade of care. In the longer term, estimating the indicators of the cascade of care requires a database of HCV-infected persons based on simple individuals' records. Such databases can be integrated with those used to monitor HIV and/or TB treatment as appropriate

CHAPTER 7. IMPROVING THE UPTAKE OF TESTING AND LINKAGE TO CARE

This chapter combines existing recommendations on three interventions to promote uptake of testing and linkage and five new or updated recommendations. The evidence base and rationale for the three existing recommendations from the 2017 WHO *Guidelines on hepatitis B and C testing (4)* are summarized below. The evidence base and rationale for the new recommendations are covered in the relevant chapters 5, 6, 8 and 9.

7.1 Summary of existing and new recommendations on improving uptake of testing and linkage to care

Existing recommendations from 2017 WHO *Guidelines on hepatitis B and C testing (4)*

- All facility- and community-based hepatitis testing services should adopt and implement strategies to enhance uptake of testing and linkage to care *(strong recommendation, moderate certainty of evidence).*
- The following evidence-based interventions should be considered to promote uptake of hepatitis testing and linkage to care and treatment initiation:
  - peer and lay health worker support in community-based settings *(conditional recommendation, moderate certainty of evidence)*.
  - clinician reminders to prompt provider-initiated, facility-based HBV and HCV testing in settings that have electronic records or analogous reminder systems *(conditional recommendation, very low certainty of evidence)*.
  - provision of hepatitis testing as part of integrated services within a single facility, especially mental health/substance use *(very low certainty of evidence).*
  - dried blood spots for serological and virological testing *(conditional recommendation, very low certainty of evidence).*

New 2022 recommendations

- Decentralized HCV testing and treatment *(strong recommendation, moderate/low certainty of evidence)*. **New recommendation** (Chapter 5)
- Provision of hepatitis testing and treatment as part of integrated services *(strong recommendation, moderate/low certainty of evidence)*. **New recommendation** (Chapter 5)
- Task sharing of hepatitis C testing and treatment *(strong recommendation, moderate certainty of evidence)*. **New recommendation** (Chapter 6)
- Use of POC HCV RNA testing *(conditional recommendation, moderate/low certainty of evidence)*. **New recommendation** (Chapters 8 and 9)
- Reflex HCV RNA or HCV antigen testing in those with a positive HCV antibody test result[1] *(conditional recommendation, low certainty of evidence)*. **New recommendation** (Chapter 10)

[1] This can be achieved either through laboratory-based reflex viral load testing using a sample already held in a laboratory or in clinic-based reflex testing in a health facility through immediate sample collection following a positive RDT HCV antibody test.

7.2 Background

Both uptake of testing and linkage to care are essential initial components of the hepatitis C care continuum. Country-level data on the continuum for viral hepatitis care is still limited, but, as of 2019, WHO estimated that only 21% of the estimated 58 million persons with chronic HCV infection have been diagnosed and 13%, treated. The proportions are even lower in LMICs and among vulnerable populations, such as people who inject drugs, sex workers and migrants. Poor linkage to care and loss to follow-up after a diagnosis of hepatitis C is a further challenge, contributing to a steep fall-off in the continuum between diagnosis and treatment. Also, those who test negative, if at continuing high risk, as well as those who test positive, need linkage to prevention services and HBV vaccination. Without linkage to prevention, treatment and care, testing and learning one's hepatitis C status has limited value. Suboptimal linkage to prevention, care and treatment results in avoidable morbidity and mortality, poorer treatment outcomes, increased cost of care and preventable transmission.

Multiple factors may hinder the successful uptake of testing and linkage to care and prevention. These include patient-level factors, such as lack of social or family support and fear of disclosure, as well as structural or economic factors, such as stigma and discrimination, distance to care sites, lack of or cost of transportation and long waiting times at facilities *(189)*. Also, hepatitis C disproportionally affects individuals with comorbid mental health or substance use issues. Traditionally, services for hepatitis, mental health and substance use have been provided by separate clinicians or teams often located in separate health facilities and in tertiary care; this separation of services contributes to HCV treatment dropout and/or treatment failure *(190)*.

Optimizing the impact of effective treatments and prevention requires interventions both to expand uptake of testing and to improve linkage to care and retention across the care continuum, from initial screening to treatment initiation and viral suppression (HBV) or cure (HCV). Such interventions may vary based on the local context, including the health care delivery system, geography and target population. There are several well-established, evidence-based interventions that improve linkage to care and treatment of people who have received an HIV-positive diagnosis. These were first recommended in the 2015 WHO HIV consolidated testing guidelines *(3)* and in the 2016 updated ARV consolidated guidelines *(8)*. They may apply equally to viral hepatitis care and prevention.

The 2017 WHO *Guidelines on hepatitis B and C testing* recommended that all facility- and community-based hepatitis testing services implement strategies to enhance uptake of testing and linkage to care (strong recommendation, moderate certainty of evidence) *(4)* (see box above).

7.3 Summary of the evidence for three 2017 recommendations to promote testing and linkage

In 2017, WHO recommended adoption of these strategies *(4)*:

- trained peer and lay health worker support in community-based settings (moderate certainty of evidence);
- clinician reminders to prompt provider-initiated, facility-based HCV testing in settings that have electronic records or analogous reminder systems (very low certainty of evidence);
- provision of hepatitis testing as part of integrated services within a single facility, especially mental health/substance use (very low certainty of evidence).

Evidence supporting these strategies was collected in a systematic review of the impact of different interventions to enhance five key steps along the continuum of care for chronic viral hepatitis – screening, linkage to care, treatment uptake, treatment adherence and, ultimately, viral suppression. The review included 54 studies, of which 37 addressed interventions and outcomes across the HCV care continuum; 15, across the HBV care continuum; and two, across both *(191)*. Thirty-three studies were included in a meta-analysis that generated pooled effect size estimates for different outcomes. Interventions to address adherence, viral suppression and uptake of HCV testing were the best studied, but there were few methodologically rigorous studies of promoting linkage to car. All studies except one *(192, 193)* were in high-income countries. Most existing studies were judged to be of low or very low methodological quality, because of risk of bias due to study design issues, and there was a high degree of heterogeneity of outcomes across studies.

7.3.1 Clinician reminders to prompt HCV testing during clinical visits

Unlike interventions to increase HBV testing, which were primarily delivered in community settings, all 11 of the interventions to increase HCV testing either targeted health care providers or took place at established health care facilities *(191, 200-209)*. Reminder stickers attached to patient charts or in an electronic medical records system prompted providers to order HCV tests if patients belonged to a high-risk birth cohort *(204)*, reported risk behaviour *(207)* or both *(203)*. These studies found that clinician reminders to prompt HCV screening during clinical visits substantially increased HCV testing rates compared with no clinician reminders (RR = 3.70 [95% CI: 1.81–7. 57]). The certainty of evidence was rated as very low.

7.3.2 Integrated care between mental health and HCV treatment specialists

Several studies evaluated interventions providing "coordinated", "integrated", or "multidisciplinary" care to improve treatment adherence and viral suppression in patients with mental health issues *(201, 210-215)*. Three RCTs demonstrated that interventions facilitating referral to specialist sites and scheduling of visits increased patient attendance at HCV specialist visits (RR = 1.57 [95% CI: 1.03– 2.41], moderate-quality evidence). Individually tailored mental health counselling and motivational therapy to treat mental health and/or substance use issues also increased the number of patients who were regarded as eligible for treatment when compared with usual care (OR = 3.43, 95% CI: 1.81–6.49). Coordinated care between mental health and hepatitis treatment specialists along with psychological therapy and counselling for patients with mental health and/or substance use comorbidities, increased HCV treatment initiation (OR = 3.03 [95% CI: 1.24–7.37]), improved treatment completion (RR = 1.22 [95% CI: 1.05–1.41]) and increased SVR12 (RR = 1.21 [95% CI: 1.07–1.38]) when compared with usual care. Nurse-led therapeutic educational interventions also improved treatment completion and increased SVR12. The certainty of evidence was rated as low to very low.

7.3.3 Interventions to promote linkage to care for HIV

There are several well-established, evidence-based interventions that improve linkage to care and treatment of people who have received an HIV-positive diagnosis. The WHO 2015 HIV consolidated guidelines on HIV testing services *(3)* and the 2016 ARV consolidated guidelines *(8)* recommended these interventions.

7.4 Rationale for the 2017 recommendations for three strategies to promote testing and linkage

In recommending the three strategies to promote testing and linkage, WHO in 2017 considered the following rationales *(4)*.

7.4.1 Balance of benefits and harms

The Guidelines Development Group recognized that poor uptake of viral hepatitis testing and linkage to care are major barriers to access to care and treatment. To expand access to testing and treatment, programmes need not only to make use of multiple testing approaches at facility and community levels, but also to adopt interventions to promote optimal linkage to prevention and treatment. The Guidelines Development Group made a strong general recommendation for the adoption and implementation of a series of relatively simple, low-cost but effective strategies – promotion of testing by lay health workers, clinician reminders, and coordinated care between hepatitis and mental health specialists – to enhance uptake of hepatitis testing and linkage to care, although the specific recommendations were based on generally low-quality evidence.

Specifically, promotion of clinician reminders to prompt HCV screening during clinical visits increased HCV testing rates. Coordinated care between hepatitis and mental health specialists along with psychological therapy and counselling for patients with mental health and/or substance use comorbidities also increased HCV treatment initiation and treatment completion and resulted in higher SVR rates. Integration of services among certain populations of individuals with HCV, such as people who inject drugs, may also be useful. The Guidelines Development Group also considered evidence from recent systematic reviews on interventions to improve linkage to care following HIV testing, which was considered relevant to hepatitis care and treatment services.

7.4.2 Feasibility, acceptability, and resource use

Education and support for peer and lay health care workers. The findings are consistent with the growing body of evidence demonstrating that lay health workers *(1)* effectively perform a range of interventions that would otherwise be undertaken by trained medical personnel, *(2)* strengthen service delivery capacity in a variety of clinical settings in LMICs (125, 216-218) are critical to supporting decentralization of services and non-facility-based testing. Evidence supports such peer-led interventions as feasible and acceptable to both those individuals screened and lay health workers themselves *(219)*. The low cost of this intervention could facilitate its use in resource-limited settings. The lay health workers in the seven studies received training in order to help tailor the educational intervention; this training component was relatively simple and low-cost.

Clinician reminders. Clinician reminders are consistent with the broader shift towards standardizing clinical practice, including provider-initiated screening and systems-based

approaches to improving clinical outcomes. Implementation is relatively easy, and similar systems have proved effective for multiple disease modalities, such as breast *(220)* and colorectal cancer screening *(221)*.

Integrated care. Integrating HCV screening and treatment with mental health and substance use services is feasible and acceptable to targeted clients *(222, 223)*. While the interventions addressing multidisciplinary or integrated care in the evidence review were diverse, a likely key contributor to improved outcomes was co-location and coordination of services.

7.4.3 Costs and cost–effectiveness

None of the studies identified in the systematic review reported estimates of the direct cost or cost–effectiveness of interventions. However, effective linkage to hepatitis care and treatment following a positive diagnosis would be expected to improve programme effectiveness, support earlier treatment initiation and reduce loss to follow-up before treatment initiation, thus saving costs along the continuum of care.

7.5 Implementation considerations

Policies on linkage to care. Proactive linkage approaches are a critical component of comprehensive hepatitis testing services. Countries should ensure that they have specific policies and strategies to improve and prioritize linkages among hepatitis testing and prevention, treatment and care services. Interventions that strengthen multiple steps along the care continuum will generally be most efficient. The effectiveness of linkage will vary for different testing approaches.

Linkage to prevention services. As for HIV *(224)*, a range of prevention services should be available for those diagnosed with hepatitis, as well as for those who test negative. Linkage to harm- reduction services for people who inject drugs testing HCV negative is not well documented or studied. Supporting linkage to prevention services is particularly important for those with high ongoing risk, such as people who inject drugs and serodiscordant couples.

Monitoring and evaluation. Monitoring people's linkage following hepatitis testing is critical to strengthening the treatment and prevention cascades. The success of linkage should be measured by enrolment in care and not by intermediate process indicators such as the number of referrals issued. Areas for improvement should be identified. Without strategies that ensure linkage and enrolment in care, the effect of hepatitis testing in reducing HBV or HCV transmission, morbidity and mortality cannot be fully realized.

Updated WHO *Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations* were published in July 2022. These guidelines include a new recommendation on peer navigators to support people from key populations to start HIV, viral hepatitis or STI treatment and remain in care, as well as a new recommendation on offering online delivery of HIV, viral hepatitis and STI services to key populations as an additional option.

HCV DIAGNOSTICS

CHAPTER 8. DETECTION OF VIRAEMIC HCV INFECTION TO GUIDE TREATMENT – NEW RECOMMENDATIONS

8.1 Existing and new recommendations on detection of HCV viraemic infection

Existing recommendations from 2017 WHO *Guidelines on hepatitis B and C testing (4)*

Laboratory-based HCV NAT testing: Directly following a positive HCV antibody serological test result, the use of quantitative or qualitative nucleic acid testing (NAT) for detection of HCV ribonucleic acid (RNA) is recommended as the preferred strategy to diagnose viraemic infection *(strong recommendation, moderate/low certainty of evidence)*.

HCV core antigen assay: An assay to detect HCV core (p22) antigen, which has comparable clinical sensitivity to laboratory-based HCV RNA NAT assays, can be an alternative approach to diagnose HCV viraemic infection*
(conditional recommendation, moderate certainty of evidence).

New 2022 recommendation

Point-of-care (POC) HCV RNA assays: The use of HCV point-of-care (POC) RNA NAT assays can be an alternative approach to laboratory-based HCV RNA NAT assays to diagnose HCV viraemic infection *(conditional recommendation, low/moderate certainty of evidence)*.

*A lower level of analytical sensitivity can be considered if an assay is able to improve access (that is, an assay that can be used at the point of care or suitable for dried blood spot [DBS] specimens) and/or affordability. An assay with a limit of detection of 3000 IU/mL or lower would be acceptable and, based on available data, would identify 95% of those with viraemic infection.

8.2 Background

Detection of antibodies to HCV is used to determine current or past HCV infection (that is, exposure to HCV infection) and therefore to triage those who require further evaluation to determine if active viral replication is present. Between 15–45% of persons who are infected with HCV will spontaneously clear the infection *(11, 225)*. These persons remain HCV antibody positive, but they are HCV RNA negative and no longer infected with HCV. Diagnosis of viraemic HCV infection in those who are HCV antibody positive will distinguish persons with viraemic HCV infection and in need of treatment from those who have cleared the infection *(226, 227)*.

This diagnosis is generally made using NAT technologies to detect HCV RNA, but alternatives to laboratory-based NAT assays are to detect HCV core (p22) antigen or to use POC NAT or other assays, which are potentially less costly and can be used at the point of care.

Laboratory-based HCV RNA nucleic acid testing (NAT)

Both quantitative and qualitative methods are available for the detection of viraemic HCV infection. Quantitative NAT has been widely used for measuring HCV RNA levels and identifying those in need of treatment, as well as for assessing treatment response *(4, 228, 229)*. Qualitative NAT allows for rapid and sensitive detection of the virus as well as evidence of a decline in viral RNA level below a defined threshold. There are currently five commonly used quantitative HCV RNA (viral load) assays that operate on close NAT analyzers that are commercially available, with others in the research and development pipeline *(62, 230)*[1]. Although NAT technologies are very sensitive and specific for the detection of viraemia, they require a dedicated analyzer or sophisticated laboratory equipment and skilled staff. Assays to detect HCV RNA that may be used at or near the point of care have recently become commercially available. A comprehensive review of the HCV diagnostics landscape was undertaken by Unitaid in 2019 and the Clinton Health Access Initiative in 2021 *(62, 230)*.

HCV core (p22) antigen testing

In addition to using NAT, it is possible to assess for viraemic infection by testing for HCVcAg, an HCV nucleocapsid peptide 22 that is released into the plasma during viral assembly and can be detected both early on and throughout the course of HCV infection *(231)*. Serological methods that test for detection of HCVcAg have the potential to be less costly and more decentralized than NAT, but to date their uptake has been limited in low-resource settings. There are now several assays commercially available for stand-alone detection of HCVcAg *(232)*. Detection of HCVcAg has also been used as an additional marker in a fourth-generation HCV Ag/Ab serological assay because HCVcAg is detectable earlier than antibodies to HCV. However, the addition of core antigen was intended to increase sensitivity of the assay in early infection in the context of blood and blood products (and tissue) screening, and not to differentiate seropositivity from viraemic HCV infection.

POC HCV RNA NAT testing

To date, laboratory-based NAT testing has generally been the standard-of-care assay for HCV RNA detection and quantitation *(233)*. However, the high cost of these assays and laboratory requirements means that they are not readily available in resource-limited settings. As of 2022, WHO one prequalified POC HCV RNA assay[1]: the Xpert HCV Viral Load (Cepheid, USA) *(234)* ((a Xpert HCV Viral Load for fingerstick specimens assay is proceeding through WHO PQ)) *(235, 236)*. Molbio (India) also has a commercially available assay, the TrueNat HCV RNA. Molecular POC NAT options continue to increase. Existing analyzers platforms may expand test menus to HCV, while future platforms and analyzer platform-free products may launch HCV assays. Since 2021 WHO now also recommends POC assays for early HIV infant diagnosis and for HIV treatment monitoring *(230)*. WHO prequalified POC IVDs for HIV infant diagnosis and HIV viral load in 2016.

[1] https://unitaid.org/assets/HepC-Dx-Tech-Landscape_May 2019.pdf and PQ public reports, HCV: https://extranet.who.int/pqweb/vitro-diagnostics/prequalification-reports.

8.3 Summary of evidence – POC HCV RNA NAT assays

8.3.1 POC HCV RNA NAT assays (Web Annex C)

A systematic review and meta-analysis addressed the question: Does point-of-care HCV RNA testing increase the uptake of HCV RNA testing and HCV treatment initiation, and reduce time to test results and treatment initiation in HCV antibody positive persons, compared with laboratory-based standard-of-care approaches? The review covered 45 studies comprising 27 364 persons who had HCV RNA tests. Of these, 28 studies were conducted among people who inject drugs/homeless populations; four studies were among prisoner populations; nine were among general/mixed populations; and four were among people living with HIV. All 45 studies were observational in design (37 prospective and eight retrospective); there were no RCTs. The 45 included studies had a total of 64 within-study arms for analysis, of which 42 studies (45 arms) used either on-site (Model 1) or mobile (Model 2) POC RNA assays; five studies (six arms) used a laboratory-based POC assay or near POC assay (Model 3); and 12 studies (13 arms) used a laboratory-based high-throughput non-POC assay (Model 4). All analyses were also stratified by model of care (full, partial or no decentralization) to optimize comparability. Fourteen studies had direct within-study comparisons between a POC assay arm and a laboratory-based assay arm of HCV RNA – four studies with testing uptake as the end-point and ten studies with treatment uptake as the end-point. The risk of bias was high for 36% of studies and moderate for 40%. Heterogeneity was considerable (I2 >75%) for almost all study groups for each outcome.

Outcomes – turn-around time (TAT)

The pooled median TAT between HCV antibody testing and DAA treatment initiation was shorter with POC HCV RNA NAT assays on site (18.5 days [95% CI: 14–53]) than with either lab-based near POC HCV RNA NAT assays (64 days [95% CI: 64–64]) or lab-based high-throughput HCV RNA NAT assays (67 days [95% CI: 50–67]). Most (84%) of this difference was accounted for by differences in the pooled TAT from HCV RNA testing to treatment initiation. The 19 study arms that used POC HCV RNA assays had the shortest pooled TAT from HCV RNA test to treatment start: 13 days [95% CI: 10–14] in 17 arms (n=4010) with onsite POC HCV RNA assays and 0 days (that is, same-day treatment initiation) [95% CI: 0–1] in two arms (n=77) with POC HCV RNA assays in mobile units. By comparison, TATs for lab-based testing arms averaged 62 days [95% CI: 5–62] in four arms (n=2514) with lab-based near POC HCV RNA assays and 43 days [95% CI: 31–107] in five arms (n=896) with lab-based high-throughput RNA assays.

Outcomes – HCV RNA testing uptake and treatment uptake

In the studies that directly compared testing uptake between a POC assay arm and a laboratory-based assay arm of HCV RNA NAT assays, the pooled relative risk for testing uptake (four studies) was 1.11 [95% CI: 0.89–1.38] and, for treatment uptake (10 studies) was 1.32 [95% CI: 1.06–1.64], indicating better outcomes for POC assay arms. For all population groups combined, the percentage of participants initiating treatment in arms with onsite POC HCV RNA NAT assays (Model 1) was 77% [95% CI: 72–83%) (34 arms, n=23 705) and, when the POC assay was conducted in a mobile unit (Model 2), 81% [95% CI: 60–97%] (five arms, n=231).

By comparison, 89% initiated treatment [95% CI: 66–100%] when a lab-based near POC HCV RNA NAT assay was used (Model 3) (five arms, n=4758), but only 53% [95% CI: 31–75%] when a lab-based high-throughput HCV RNA NAT assay was used (Model 4) (12 arms, n=5820) p value=0.03 for models 1 and 2 versus model 4.

The key limitation of this review was the relatively few studies with direct within-study comparisons between a POC assay arm and a lab-based assay arm (four studies for HCV RNA NAT testing uptake and ten studies for treatment uptake) and the absence of any RCTs. Although we tried to carefully categorize all studies according to the four different models of care, there was still considerable heterogeneity among these care models, as well as among study populations.

8.3.2 Diagnostic accuracy[1]

A complementary systematic review and meta-analysis were undertaken to determine the diagnostic performance (sensitivity and specificity) of POC HCV RNA NAT assays compared with laboratory-based NAT assays. A total of 25 studies were included, comprising data from 8791 patients. Of these, 16 studies evaluated Xpert HCV RNA assay (Cepheid, USA); six studies, the Xpert HCV VL Fingerprick (Cepheid, USA); six studies the Genedrive HCV ID Kit (Genedrive Diagnostics Ltd, UK), two studies Truenat HCV assay(Molbio Diagnostics Pvt. Ltd, India), and one study the SAMBA II HCV Qualitative Whole Blood Test (Diagnostics for the Real World, UK). Eleven studies used finger-prick capillary whole blood, 17 studies used serum or plasma, and four used venous whole blood. Sixteen studies used freshly collected specimens, and nine used specimens stored at -20 °C. Twelve studies took place in high-income countries, and 13 were in LMICs. Across all assays, the pooled sensitivity was 99% [95% CI: 98–99%] and specificity was 99% [95% CI: 99–100%] relative to a lab-based reference standard. High sensitivity and specificity were observed across all study settings and populations in both LMICs and high-income countries and across different assays and specimen types.

8.3.3 Additional, supporting evidence from HIV and other diseases

WHO has previously recommended use of POC NAT molecular assays for the rapid first-step identification of rifampicin-resistant and multidrug-resistant TB and for routine diagnosis of TB *(237)*. In 2021 WHO also recommended use of POC HIV RNA NAT assays for early infant diagnosis of HIV and routine HIV viral load monitoring for people living with HIV on ART *(166)*. For early infant diagnosis (EID), this was based on high certainty data from RCTs and large well-characterized cohorts showing that POC EID infant testing was associated with faster delivery of results and faster ART initiation in HIV-positive infants *(166)*. Infants who received POC testing were eight times more likely to start treatment within 60 days of initial sample collection than those whose blood samples were sent to laboratories (92.8% versus 50.5%; OR=7.9, p<0.001). Same-day treatment initiation was 51% with POC versus none with standard-of-care *(238)*. Similarly, POC HIV viral load testing for monitoring resulted in faster return of results to patients [same-day versus 28 days, HR 17.7 (13.0–24.2)] and to clinicians (HR 11.7), and shorter time to clinical action for elevated VL [same-day versus 76 days, HR 10.9 (2.1–57.5)] than standard-

[1] Tang W, Tao Y, Fajardo E, Reipold EI, Chou R, Tucker JD, Easterbrook P. Diagnostic Accuracy of Point-of-Care HCV Viral Load Assays for HCV Diagnosis: A Systematic Review and Meta-Analysis. Diagnostics (Basel). 2022 May 18;12(5):1255. doi: 10.3390/diagnostics12051255. PMID: 35626411; PMCID: PMC9141110.

of-care comparators *(239)*. These findings on impact of use of POC HIV RNA assays on turn around time and time to treatment for EID in children and in HIV treatment monitoring provides further indirect evidence to support their use in HCV infection.

8.4 Rationale for the recommendations – POC HCV RNA NAT assays

8.4.1 Balance of benefits and harms

The Guidelines Development Group recognized that access to laboratory-based NAT assays is limited in resource-limited settings and that this poses an important barrier to treatment. For several reasons the Group made a conditional recommendation to consider use of POC RNA NAT assays as an alternative to laboratory-based RNA NAT or HCV core antigen assays to diagnose viraemic HCV infection, based on moderate-/low-quality evidence:

1. HCV RNA POC platforms can be used in lower levels of health facilities, given their relative ease-of-use and suitability for running single tests without the need to batch test runs. These assays thereore offer an opportunity to confirm viraemia near to where patient is receiving care.
2. POC HCV RNA NAT assays can to lead to greater uptake of and faster testing, and shorter time from testing to return of results to the clinician and treatment initiation, especially when used in fully decentralized care models ie. where testing and treatment are available at the same site and potentially on the same day. Where patients need to travel to another site for treatment, overall time to treatment is prolonged regardless of the use of POC RNA assays.
3. OIC NAT molecular platforms are already on the market for a number of infectious diseases, including SARS-CoV-2. They are recommended by WHO for HIV EID and ART monitoring *(166)* and TB diagnosis, including diagnosis of drug-resistant TB *(240)*. The availability of multi-disease testing devices offers potential for integration of HCV RNA testing that may further expand access while achieving significant system efficiencies and cost-savings. POC testing may reduce some operational needs (e.g. specimen transport, and central result return systems).
4. The majority of currently available POC HCV RNA NAT assays have high sensitivity and specificity and similar LoD to laboratory-based NAT assays. POC NAT assays can also be used both for HCV diagnosis and as a test of cure.

There are no notable harms with POC HCV testing, but there are several important challenges:

- POC platforms have more limited test throughput compared to laboratory-based platforms. Therefore, depending on daily specimen/patient volumes, health care facilities may need to prioritize who should receive PoC testing results so immediate treatment and care decisions can be made.
- There are still few manufacturers of POC HCV RNA NAT assays and, therefore, limited competition to drive down costs and options for country selection.
- Monitoring, supervision, training, quality assurance and maintenance of a large number of devices would be challenging.

- There are specific requirements of high-temperature incineration for safe waste disposal of guanidinium thiocyanate (GTC) which is contained in some assays, including those for GeneXpert.

8.4.2 Acceptability, values and preferences (Web Annex D)

In a multi-country online survey of 210 people in 49 countries undertaken by the World Hepatitis Alliance and Coalition Plus, 88% of participants confirmed a strong preference to "do your initial and confirmatory viral load tests on the same day". This preference was even higher, at 96%, among people who currently inject or formerly injected drugs. The main reasons given for this preference were the opportunity to more rapidly confirm diagnosis (81%) and start treatment (76%). There was also a strong preference, from 93% of respondents, to do both the initial screening test and confirmatory viral load testing at the same place, largely for reasons of convenience (70%), and at a community-friendly site (60%).

8.4.3 Cost-effectiveness of POC HCV RNA assays

Three studies provided robust cost-effectiveness analyses that compared the use of POC and non-POC HCV RNA NAT assays. All three found POC HCV RNA NAT assays to be cost–effective compared with laboratory-based HCV RNA assays *(241, 242)*. Two studies used a decision tree model to compare, from a health sector perspective, 12 testing strategies among various population groups in Cameroon, Côte-d'Ivoire and Senegal *(243)* and among people who inject drugs in Senegal *(244)*. They found that a strategy combining an HCV antibody RDT and RNA testing was cost-saving compared with all other strategies except when HCV antibody RDT testing was combined with laboratory-based HCV RNA NAT, which was expensive in all settings. The HCV antibody RDT and HCV RNA test strategy cost the least per person screened (€ 8.18). By comparison, the POC HCV RNA NAT only strategy cost € 14.28 per person screened; the anti-HCV RDT and laboratory HCV-RNA NAT (DBS) strategy cost € 10.69 per person; and the anti-HCV RDT and lab HCV-RNA NAT (venepuncture whole blood) strategy cost € 10.45. The HCV antibody RDT and POC HCV RNA NAT strategy was cost-saving compared with all other strategies considered in terms of cost per true positive case detected, except for the HCV antibody RDT and laboratory-based HCV RNA NAT (venepuncture whole blood) strategy, for which the incremental cost–effectiveness ratio (ICER) per true positive case detected was € 1895.29. This ICER rose when loss to follow-up due to patients' reluctance for venepuncture was considered, indicating that the HCV antibody RDT and POC HCV RNA NAT strategy was optimal. The study in Senegal among people who inject drugs yielded similar results *(244)*. However, these two studies assessed cost–effectiveness in terms of ICER per true positive diagnosis and so may miss further benefits of POC HCV RNA NAT assays seen farther down the HCV cascade of care through reductions in loss to follow-up. A study in prisons in England, United Kingdom, assessed outcomes in terms of ICERs per quality-adjusted life year (QALY) gained. Results ranged between £ 3565-£ 10 300, below the national willingness-to-pay threshold of £ 30 000 *(242)*.

8.4.4 Equity

POC HCV RNA NAT assays would promote equity if used in settings and populations at high risk of loss to follow-up, which would particularly benefit from the convenience of POC testing and a rapid test-and-treat approach, such as the homeless and people who inject drugs at harm reduction sites and in prisons. In the systematic review, among people who inject drugs/homeless populations, there was increased HCV RNA NAT testing uptake with use of POC RNA assays on site (93% [95% CI: 83–99%]) or in mobile units (84% [95% CI: 43–100%]) compared with lab-based high-throughput HCV RNA assays (27% [95% CI: 18–38%]). Similarly, among prisoners there was evidence of increased treatment uptake with use of POC HCV RNA NAT assays on site (89% [95% CI: 67–100%]) compared with laboratory-based high-throughput HCV RNA assays (20% [95% CI: 14–26%]). The introduction of multidisease testing devices (polyvalent testing platforms) brings additional potential for integration that may further expand access and achieve significant system efficiencies and cost-savings.

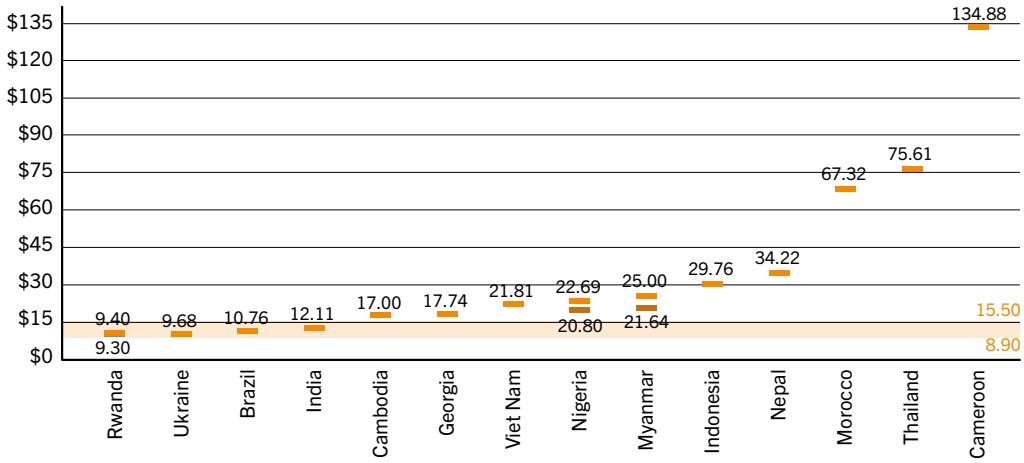
8.4.5 Feasibility

A 2017 survey of hepatitis testing experience in 19 LMICs found that around 40% of respondent countries did not have access to laboratory-based HCV RNA NAT assays for HCV diagnosis in their countries *(121)*. POC testing programmes using similar platforms have been successfully deployed in multiple countries for other uses, such as HIV EID testing, HIV viral load monitoring and TB diagnosis. Countries with existing multi-disease platforms for HIV VL testing or TB, and those that are planning for their introduction may consider collaboration and integration of HCV VL testing *(186)*. This includes both high-throughput laboratory-based instruments for HIV VL and/or HCV RNA measurement and POC instruments for HIV and TB. There is one supplier with WHO-prequalified products (Cepheid). Molbio (India) has a commercially available assay: Truenat HCV RNA, and a Cepheid fingerstick assay is undergoing WHO Prequalification. Molecular POC options continue to increase and should be encouraged.

8.4.6 Resource considerations

Programmes report varied final costs for HCV RNA assays (Figure 8.1), with many LMICs achieving prices around US$ 10 to $ 30 per HCV RNA test (both centralized laboratory-based and POC testing). The device costs as well as costs associated with operational components should also be considered. Programmes with higher volumes and pooled procurements (including with other disease assays) may achieve lower costs. In the future, increased competition may both increase access and decrease pricing.

FIGURE 8.1 HCV RNA price per test (in US$) paid by public programmes



Data collected in 2020–2021 as final prices paid by public programmes for any HCV VL assay (POC or centralized)
Source: Clinton Health Access Initiative. HCV market intelligence report, 2021 *(62)*

8.5 Summary of the evidence – laboratory-based HCV RNA NAT assays from 2017 hepatitis testing guidelines *(4)*

In 2017, WHO recommended quantitative or qualitative NAT for detection of HCV RNA as the preferred strategy to diagnose viraemic infection following a positive HCV antibody test result *(4)*.

For the 2017 WHO *Guidelines on testing for viral hepatitis B and C*, two systematic reviews were undertaken that evaluated the diagnostic accuracy for detection of viraemic HCV infection of (i) qualitative versus quantitative NAT and (ii) HCVcAg testing versus NAT *(245)*.

Diagnostic accuracy and limit of detection

HCV NAT assays

One of the systematic reviews identified four eligible studies *(246-249)* that compared the performance of three quantitative HCV RNA NAT assays with that of a reference qualitative NAT (two assays used). Although early-generation qualitative NAT assays were able to detect the presence of HCV in plasma at concentrations a full log lower (that is, about 10-fold less) than quantitative NAT assays, the lower limit of quantification of new versions of quantitative assays is now comparable to that of most commercial qualitative assays (that is, 15 IU/mL).

HCVcAg assays

There were 50 studies that evaluated seven commercial HCV cAg assays. There was significant variation in performance among the different assay brands (Table 8.1) *(245)*.The pooled sensitivity and specificity with 95% CIs were: ARCHITECT HCV Ag (DENKA SEIKEN CO., LTD., Japan for Abbott GmbH & Co. KG, Germany) sensitivity 93.4% (95% CI: 88.7–96.2) and specificity 98.7% (95% CI: 96.9–99.4); ORTHO® HCV Version 3.0 ELISA Test System (Ortho-Clinical Diagnostics, Inc, USA) sensitivity 93.2% (95% CI: 81.6–97.7) and specificity 99.2% (95% CI: 87.9–100); and Hunan Jynda sensitivity 59.5% (95% CI: 46–71.7) and specificity 82.9% (95% CI: 58.6–94.3). The sensitivity of the Fujirebio Lumipulse HCV Ag was 95% (95% CI: 90.2– 99.8) in one study, but specificities could not be calculated.

The estimates for the ARCHITECT HCV Ag assay were more homogeneous and precise, as this assay has been the most extensively studied. A pooled quantitative analysis of data available from three studies demonstrated a close correlation between HCV Ag and HCV RNA at viral HCV RNA concentrations above 3000 IU/mL. The LoD for the most sensitive assay is 3 fmol/L HCV Ag or 0.06 pg/mL, which equates to a LoD of ~1000–3000 IU/mL by NAT and is consistent with the analytical sensitivity (LoD) reported by the manufacturer. HCV RNA NAT assays are considered the reference standard for the detection of viraemia, but the quality of studies comparing quantitative and qualitative assays for detection of viraemia was rated as low because of small numbers of studies and heterogeneity in populations. The overall quality of the evidence for the recommendation to use HCV cAg was rated as low to moderate because of inconsistency and imprecision.

Limit of detection (LoD). A multi-cohort analysis examined the distribution of HCV RNA levels at diagnosis in 66 640 individuals in 12 countries and established that 97% and 95% had an HCV RNA level greater than 1318 IU/mL and 3311 IU/ml, respectively *(250)*. WHO pre-qualified laboratory-based NAT assays (Abbott Real Time HCV PCR (Abbott Molecular Inc, USA), and Alinity mHCV RT-PCR (Abbott Molecular Inc, USA) and Roche cobas HCV (Quantitative nucleic acid test for use on cobas 6800/8800 Systems. These assays have a broad dynamic range, from 12 to 7 700 000 IU/mL, and the reviews showed analytical sensitivity as low as 5 IU/mL for qualitative HCV RNA by NAT. The LoD of POC HCV RNA NAT assays are 10 IU/mL for GeneXpert using venous blood *(251, 252)* or 100 IU/mL using fingerstick capillary blood. The Genedrive instrument has reported a LoD of 2362 IU/mL *(253)*. The HCV core antigen assay LoD is 1000–3000 IU/mL. All assays are, therefore, acceptable for diagnosis of HCV viraemic infection.

TABLE 8.1 Summary of diagnostic accuracy of HCV core antigen assays compared with NAT

INDEX TEST	SAMPLE SIZE (RANGE)	DIAGNOSTIC ACCURACY (95% CI)	
		Sensitivity	Specificity
Abbott Diagnostics GmbH, Architect HCV Ag Assay	20 (11—820)	93.4% (88.7—96.2)	98.7% (96.9—99.4)
Ortho-Clinical Diagnostics Ortho ELISA-Ag	5 (1—177)	93.2% (81.6—97.7)	99.2% (87.9—99.9)
Bio-RAD Monolisa HCV Ag-Ab ULTRA	5 *(525)*	28.6—95%[a]	94.9% (89.9—99.8)[b]
EIKEN Lumispot HCV Ag	2 *(235)*	97.5—98.1%[a]	ND
Fujirebio Lumipulse Ortho HCV Ag	1 *(80)*	95% (90.2—99.8)[b]	ND
Hunan Jynda HCV Core Ag ELISA	4 *(524)*	59.5% (46—71.7)	82.9% (58.6—94.3)
DiaSorin S.A. Murex HCV Ag/Ab	4 *(730)*	50—100%[a]	83.8—100%[a]

CI = confidence interval; ND = no data
[a] Meta-analysis not possible. Range of results seen across studies reported.
[b] Result from one study only.

8.6 Rationale for the recommendations – laboratory-based HCV RNA NAT assays from 2017 hepatitis testing guidelines *(4)*

8.6.1 Balance of benefits and harms

Use of laboratory-based quantitative or qualitative NAT assays for detection of HCV RNA

In 2017, for the WHO *Guidelines on testing for viral hepatitis B and C*, the Guidelines Development Group made a strong recommendation for the use of an NAT assay (either qualitative or quantitative) as the preferred strategy for diagnosis of viraemic HCV infection, based on moderate-/low-quality evidence, for several reasons:

1. The new generation of quantitative and qualitative assays for HCV RNA NAT assays have the same LoD, which is around 15 IU/mL. However, quantitative assays are a reproducible method to detect and quantify HCV RNA in plasma or serum.
2. A multi-cohort analysis showed that that 95% of those with chronic infection have an HCV RNA level >3000 IU/mL *(250)*. Therefore, the range of clinically observed HCV RNA concentrations in serum is rarely below the lower range of the limit of quantification of quantitative assays, and most NAT assays (quantitative or qualitative) will capture the majority of viraemic infections as well as treatment failures.

3. Although quantitative RNA NAT assays are considered the gold standard assays for the diagnosis and monitoring of HCV, the high cost of these assays and laboratory requirements mean that they are not readily available in resource-limited settings. NATs for use at or near the POC for quantitation of HCV RNA are now recommended as additional approach (especially for hard-to-reach populations and in remote settings) for countries to consider in their plans for national testing/diagnostics infrastructure and national viral hepatitis strategic plans.

Use of laboratory-based HCV core antigen for detection of viraemic HCV infection

The Guidelines Development Group recognized that there is limited access to HCV RNA NAT assays in resource-limited settings and that this poses an important barrier to antiviral treatment. The Group made a conditional recommendation to consider use of HCV cAg assays as an alternative to HCV RNA NAT to diagnose viraemic HCV infection, based on moderate-quality evidence, for several reasons:

1. HCV cAg assays can utilize existing serological testing platforms and potentially cost less than NAT. They could serve as a more affordable replacement for HCV RNA NAT for diagnosis of viraemic HCV infection in the future.
2. Although HCV cAg testing is currently limited to only a few platforms and even those with the highest performance do not reach the sensitivity of HCV RNA NAT, some well-performing HCV cAg assays have high sensitivity (up to 93.4% for certain commercial assays) and high specificity (>98%), and good correlation with HCV RNA to an LoD above HCV RNA levels of 3000 IU/mL, which will detect over 95% of chronic HCV infections. However, there was wide variation in sensitivity/specificity between assays and also within the same brand of assay for all but the Abbott ARCHITECT.
3. HCV cAg assays also offer the potential in the future to be applied as a one-step screening assay, as HCV cAg HCV cAg appears earlier than HCV antibodies (1–2 days after HCV RNA appears), has a high specificity, and so does not require confirmatory testing. However, such a strategy would be cost–effective only in very high prevalence settings.

The risk with the use of HCVcAg is that, due to the lower clinical sensitivity of the HCV Ag test, a small proportion of cases may be missed due to low circulating HCV RNA concentrations. As a result, the use of dried blood spot testing for HCV Ag is not currently feasible. A further consideration is that it is preferable, in order to simplify the diagnostic pathway, to select an assay that can be used for both diagnosis of current infection and for test of cure. On the basis of the limited current evidence, the HCV cAg assay cannot be recommended as a reliable SVR test of cure compared with HCV RNA NAT assays.

8.6.2 Acceptability, values and preferences

The values and preferences survey identified respondents' preferences for future HCV testing strategies. A key preference was for a single-step HCV diagnostic strategy with a low-cost POC test for confirming viraemic infection (48% of respondents). Of these, 52% opted for an HCV RNA NAT because of its high sensitivity, and 35% for an HCV cAg assay because of its lower cost and ease of use. More than half the respondents were prepared to compromise on sensitivity down to 95% in order to gain a reduction in the price of the test. Among the respondents, 47% preferred a test that uses capillary blood and, therefore, could be more easily performed in POC settings, even at the expense of test sensitivity. A short turnaround time (at least same-day) was another key consideration to reduce loss to follow-up, save transportation expenses and enable providers to see more patients within a day.

Participants were asked, "Would you prefer to do your initial and confirmatory HCV viral load tests on the same day?" Overall, 88% answered "yes"; among people who currently inject drugs or formerly injected drugs, 96% said "yes". The main reasons were the possibility to more rapidly confirm a diagnosis (81%) and start treatment (76%). There was also a strong preference from 93% of respondents for doing both the initial screening test and then confirmatory VL testing at the same place, for convenience (70%), and at a community-friendly site (60%).

8.6.3 Feasibility

The survey of hepatitis testing experience in 2017 in 19 LMICs found that NAT for HCV RNA was available at one third of the sites, but 40% of respondent countries did not have any access to NAT for HCV diagnosis in their countries. The HCV cAg assay was not available at any site.

8.6.4 Resource considerations

Programmes report varied final costs for HCV RNA assays – both POC and centralized laboratory testing (Figure 8.1). The resources required for quantitative NAT vary considerably, with the cost per test ranging from US$ 30 to US$ 200. Furthermore, the laboratory equipment is expensive and requires technicians with specialized training. The cost of testing for HCV cAg is currently US$ 25–50 (data from Médecins Sans Frontières). This cost is comparable to that of qualitative NAT (US$ 43–51) but still a major barrier to its use.

8.7 Implementation considerations

See also Box 8.2 Case study: Operational considerations for implementation of point-of-care HCV viral load testing in community-based HCV clinic in Yangon, Myanmar

- **Use of laboratory-based versus POC NAT platforms:** The decision whether to use POC RNA NAT technologies or laboratory assays will depend on a variety of factors, including cost and ease of use and the characteristics of the testing site, such as storage facilities, infrastructure, level of staff skills and cost. Use of POC assays may also be considered in services caring for specific vulnerable populations such as people who inject drugs or people in prisons, with high loss to follow-up or in remote locations. Although POC assays may promote and expedite confirmation of viraemia, there are also many excellent examples in which a centralized laboratory-based system has been highly effective when supported by efficient specimen transport and rapid electronic delivery of results *(254)*.
- **Priority settings for placement of HCV RNA NAT POC platforms** are likely to be where there are populations at high risk of loss to follow-up and at risk of greater morbidity, but where testing volume is not large, such as among people who inject drugs at harm reduction sites or those in prisons, where fast-tracking diagnosis and treatment initiation as soon as possible upon entry to prison increases their chance of finishing their treatment regimens before leaving prison (241, 255-257). There are other innovative strategies for delivering POC HCV RNA NAT assays to hard-to-reach populations – for example, through mobile units *(258-262)* that can offer testing and treatment initiation on the same day *(263)*. The systematic review found strong evidence that the best turn-around times and cascade of care outcomes with POC assays are seen when they are, in fact, used at the point of care rather than placed in laboratories distant from the patients.
- **The optimal placement of a POC instrument is where testing and treatment are at the same site – a "one-stop shops".** Use of POC platforms may not achieve expected outcomes if other aspects of the care pathway require patients to travel to another clinic for treatment, with associated transport and other costs. A recent systematic review (Web Annex A) has shown that one of the most important interventions to promote access and improve uptake of testing and treatment is delivery of fully decentralized HCV care *(139)*. The POC evidence review (Web Annex A) showed that the best results for use of POC assays were when they were placed in clinics where HCV testing and treatment were available at the same site, especially for people who inject drugs at harm reduction sites, among people living with HIV in ART clinics, among prisoners and in primary care.

The best results for use of POC assays were where HCV testing and treatment were available at the same site.

- **Reflex HCV RNA testing after a positive HCV antibody result:** WHO now recommends reflex HCV RNA testing of those with a positive HCV antibody test result as an additional strategy to promote uptake and reduce time to confirmation of viraemia and treatment (Chapter 9). This can be achieved either through laboratory-based reflex HCV RNA testing using a specimen already held in the lab or through clinic-based reflex testing in a health facility through immediate specimen collection for viraemic testing following a positive HCV antibody RDT result. Efforts should be made to minimalize risk of contamination when reflex testing from a stored specimen.
- **Multi-disease testing platform and diagnostic integration across programmes:** The introduction of multi-disease testing platforms, both high-throughput lab-based and POC devices, creates additional opportunities for integration that may further expand access and achieve significant system efficiencies and cost-savings. Countries with existing multi-disease platforms for HIV viral load, HIV infant diagnosis, SARS-CoV-2, or TB diagnosis or those that are planning for their introduction can consider collaboration and integration of HCV RNA testing *(186)*. Pilot programmes have demonstrated successes with lab-based and POC HIV/TB and HIV/HCV integration *(264)*. Diagnostic network optimization and integrating platforms across disease areas (HIV, TB, SARS-CoV-2, HCV) can improve rational utilization of existing capacity and save costs.

BOX 8.1 Operational considerations for use and maintenance of POC assays

- **Both centralized laboratory and POC testing require strong decentralized systems** (for example, quality control assurance, platform service and maintenance, efficient supply chain, trained staff, ongoing mentorship and waste disposal). The use of POC technologies in particular should consider how specimen collection and processing and results return can be integrated the patient care pathway.
- **The infrastructure required for POC platforms will depend on the device and assay and should be reviewed and installed prior to implementation.** Near POC technologies will generally require a sturdy table for centrifugation (not required for fingerstick), air-conditioning for temperature control, a room with a sealed door to minimize dust, clinical waste disposal bins and access to a sink with running water for basic laboratory cleaning and accident management. If electricity is unstable and interrupted, an online uninterruptable power supply (UPS) and voltage stabilizer are required for the Xpert device.
- **Stock management** requires accurate monitoring of current stock and upcoming expiry dates and demand forecasting to ensure regular supplies of diagnostic without wastage. Cartridges/reagents for POC HCV RNA generally have a shelf life of 12 months from manufacture.

- **Regular internal quality control (IQC) and external quality assessment (EQA)** checks to ensure the assay works properly (quality control) and that the testing service can return the correct result (external quality assessment). Any issues with the product should be reported to the assay manufacturer as part of their post-market surveillanceappropriate use of the PoC device and identify errors.
- **Storage and transport:** Xpert cartridges/reagents generally require storage at 2–28°C; analysers Xpert device requires laboratory an environment at 15–30°C, stable continuous electricity supply, no direct sunlight, and an environment controlled to minimise dust and humidity
- **Staff training:** POC assays require training specific to the device used, but laboratory experience is not necessary.
- **Transport and disposal:** Assays should be transported in conditions similar to storage conditions and disposed of using proper waste management procedures, ensuring that harmful chemicals are not released into the environment. (For example, Xpert cartridges require high-temperature incineration.)

8.8 Research gaps

- The use of POC platforms for HCV and HBV diagnosis and treatment decisions needs more methodologically rigorous implementation science studies (ideally, comparative RCTs). Use of POC testing should be considered alongside other interventions to promote the uptake of viral hepatitis testing, linkage to assessment and treatment uptake, especially in LMICs. Future studies should fully describe the diagnostic platform and service delivery model, and evaluation should assess effectiveness across the entire continuum of care and not just treatment-related outcomes. Including costs would allow for comparative cost-effectiveness analyses.
- Evaluation of impact of integrated use of multi-disease testing with diagnostic platforms on access or uptake of testing, utilization of platforms, turnaround times, cost and feasibility.
- Evaluation of the diagnostic accuracy, cost, cost–effectiveness and impact of HCV cAg or HCV RNA NAT assays as a one-step diagnostic testing strategy.
- Evaluation of the concordance between whole blood samples and DBS for HCV viremia using POC HCV RNA assays, such as Xpert.

BOX 8.2 Case study: Operational considerations for implementation of point-of-care HCV VL testing in community-based HCV clinic in Yangon, Myanmar *(265, 266)*

Service delivery model

The CT2 Study was a feasibility study of a decentralized, community-based test-and-treat model of care for HCV in Yangon, Myanmar. POC testing was used for HCV diagnosis, including the Abbott® SD BIOLINE HCV (Abbott Diagnostics Korea, Republic of Korea)- an HCV antibody rapid test and the Cepheid® GeneXpert® point-of-care HCV Viral Load (Cepheid AB, Sweden)– a POC assay. General practitioners led the HCV care, with pangenotypic generic direct-acting antivirals (DAAs) prescribed to eligible participants. The feasibility study had two study sites in Yangon: one for people who inject drugs and one for people with liver disease. At each site all testing and treatment services were provided on-site in a decentralized, "one-stop shop" model of care. From January 2019 to August 2020, 633 participants were recruited; 606 received HCV VL testing; and 488 initiated DAA treatment for active HCV infection. 477 (98%) completed DAA therapy and 421 (92%) achieved SVR12. Although this study used a GeneXpert device, many of the principles and lessons learned are applicable to other POC devices.

Example of laboratory set-up (Burnet Institute Clinic)

Key operational considerations for implementation of POC HCV testing in community settings are the following:

Training

- Laboratory technicians, nurses and general practitioners received training on the device on three occasions: first, orientation;, second, on-site practical training after machine installation, provided by the local distributor before study initiation; and, and internal External Quality Assessment Scheme (EQAS) training prior to enrolment in EQAS programme.

- The laboratory technicians were primarily responsible for phlebotomy and running the device. They reported that the staggered trainings were useful, as they provided several opportunities to ask questions as the technicians became more familiar with the device. The technicians reported that, with further training, ongoing support and ongoing use of the device, they felt more confident and more familiar with the nature of errors. The HCV RNA result presented in the logarithmic scale ensured clear interpretation of the result. Nurses and general practitioners were also trained to perform the tests, but they did not maintain competency throughout the study period because they did not run tests often.
- Overall, the staff reported they found the GeneXpert analyserdevice simple and easy to operate, but that it was sensitive to errors during the specimen preparation stage. They noted that the specimen preparation (for the venous blood specimen plasma test cartridge) required precise pipetting skills to prepare the required specimen amount after centrifuging the whole blood specimen to separate plasma.

Laboratory set-up

The study was implemented in two shopfront community-based clinics (equivalent to primary care facilities), and rooms were renovated to provide laboratory services. The laboratories had the following equipment: four-module GeneXpert machine, online UPS, GeneXpert laptop, GeneXpert barcode scanner, printer, centrifuge, air-conditioner, table, chair, filing cabinet, clinical waste disposal bins, sink and running water. One site underwent renovations during the study to improve the conditions for the GeneXpert machine, including reducing the dust flowing into the room by installing a sliding door, reducing the number of people entering and leaving the room and reducing the humidity through use of an exhaust fan.

Electricity supply: The facilities were small shopfronts, with only small on-site generators to assist with power back-up. This is in contrast to hospitals or private laboratories, which often have large power back-up systems. These small generators required manual start-up in a power outage. They were used only occasionally, during power outages, due to requiring maintenance, the anticipated short duration of the power outage and fuel costs.

Yangon experiences scheduled and unscheduled power outages prior to monsoon season (April to June) and during monsoon season (June to October). One site experienced recurring errors with a GeneXpert machine due to unstable electricity supply (power outages and fluctuating voltage). The problem was resolved with installation of an online UPS providing voltage stabilizing and 1–2 hours of electricity to ensure the test cycle could be completed.

Temperature/humidity control: Daily temperatures in Yangon average a low of 17 °C and high of 32 °C but commonly reach maximum temperatures of 39 °C in March and April; humidity ranges from an average 65% in the dry season to 85% in the monsoon season. These conditions posed some challenges to test kit/reagent storage and device operations. Test kits/reagents require storage under 30 °C and could be damaged by high humidity.

Sites were advised to store test kits/reagents in the refrigerator prior to the day of use. Storage of RDT test kits and Xpert cartridges in refrigerators required substantial space. The refrigerators procured were standard household refrigerators. Laboratory refrigerators may be better suited to storage of test kit reagents and cartridge boxes and allow for easy access and stock monitoring. Cost and suitability should be considered when procuring refrigerators specifically for stock storage.

GeneXpert maintenance and module replacements: The GeneXpert devices require annual maintenance required for Xpert device, including the distributor's technical support personnel running GeneXpert checks onsite, plus ad hoc maintenance and replacements if recurrent errors occur. At both sites there were recurrent errors over a few days during the rainy season, which required installation of online UPS and voltage stabilizers to improve power supply and protect machine.

GeneXpert HCV Viral Load assay errors: The total error rate across the study was 5% of the total number of tests run, including HCV VL assays for diagnosis of active HCV infection and assessment of SVR12 (n=1137). An error was defined as any erroneous output, no result or invalid result produced when running the GeneXpert HCV viral load assay.

Quality control: Sites were enrolled in the External Quality Assessment Scheme (EQAS) Program for HCV Viral Load testing through Australia National Serology Reference Laboratory, Australia along with national laboratories in Myanmar. There were quarterly test events of which the sites participated in three events.

Sites performed minimal internal quality control (IQC) starting part way through the study period; but should be considered for future implementation. This involved weekly unblinded testing using known positive and negative specimens provided from the National Health Laboratory in Yangon or from cross-clinic specimens, which can be stored at 4 °C for a month.

Regular quality assurance checks were performed to ensure appropriate use of the Xpert device and to identify errors. Trouble-shooting of errors and recurrent issues was conducted.

External support for sites to conduct ICQ and participate in EQAS must be tailored to specific contexts and fit for purpose, considering what is feasible, affordable and practical for a government laboratory or a private laboratory to provide. Sites required some training prior to enrolment in the EQAS and assistance in preparing and uploading test event results in the required format.

Supplies: Xpert HCV viral load cartridges have a shelf life of 12 months from manufacture. For this project this generally meant a shelf life of 6–9 months after clearing customs and arriving at clinics, requiring regular supply via local distributor and accurate forecasting of demand.

CHAPTER 9. ASSESSMENT OF HCV TREATMENT RESPONSE – TEST OF CURE

9.1 Existing and new recommendations on assessment of HCV treatment response

Existing recommendations from 2017 WHO Guidelines on hepatitis B and C testing *(4)*

Laboratory-based HCV RNA NAT assays: Nucleic acid testing (NAT) for qualitative or quantitative detection of HCV RNA should be used as test of cure at 12 or 24 weeks (that is, sustained virological response (SVR12 or SVR24)) after completion of antiviral treatment

(conditional recommendation, moderate certainty of evidence)

New recommendation

Point-of-case HCV RNA assays: Point-of-care (POC) HCV RNA NAT assays with comparable limit of detection to laboratory-based assays can be used as an alternative approach as a test of cure

(conditional recommendation, low/moderate certainty of evidence)

9.2 Background

Confirmation of undetectable HCV RNA in a previously viraemic individual is important to assess the virological response to DAA treatment *(267-269)*. Prior to the introduction of curative oral DAA treatment regimens, treatment with interferon (IFN)-based regimens required frequent monitoring of HCV RNA levels during therapy to decide whether treatment should be stopped or could be shortened. These multiple assessments are now no longer relevant with the newer DAAs because of their greater efficacy and relative infrequency of viral breakthrough. In addition, the rate of HCV RNA decline is not perfectly correlated with SVR, and, indeed, in most persons treated with DAAs, HCV RNA is already undetectable four weeks after treatment initiation. A single negative (undetectable) test of HCV RNA at 12 weeks after completion of therapy (SVR12) is now the benchmark for assessing treatment outcome and cure using qualitative or quantitative HCV RNA NAT assays.

HCV cAg testing and now POC HCV RNA NAT assays are recommended as alternatives to laboratory-based HCV RNA NAT assays for the diagnosis of viraemic HCV infection. A multi-cohort analysis examined the distribution of HCV RNA levels at diagnosis in 66 640 individuals and established that 97% had HCV RNA levels greater than 1318 IU/mL, and 95% had HCV RNA levels greater than 3311 IU/ml *(250)*. WHO pre-qualified laboratory-based assays have an analytical sensitivity as low as 12 IU/mL and 5 IU/mL LoD for qualitative HCV RNA by NAT. The LoD of POC HCV RNA assays are 10 IU/mL for GeneXpert using venous blood *(251, 252)* and 100 IU/mL with fingerstick capillary blood. The reported lower limit of detection (LoD) for the Genedrive instrument is 2362 IU/mL *(253)* and for core antigen assay is 1000–3000 IU/mL. All assays are, therefore, acceptable for diagnosis of HCV viraemic HCV infection.

However, it needs to be established whether HCV cAg and POC HCV RNA assays can also be used for assessing a sustained response to HCV antiviral treatment and, therefore, as a test for cure. Currently, the European Association for the Study of the Liver Diseases and the American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) HCV guidance panel recommend a minimum LoD of 1000 IU/mL for HCV diagnosis, but neither yet specifies minimal performance characteristics for test of cure *(270)*.

9.3 Summary of the evidence[1]

Based on results of the earlier multi-cohort analysis mentioned above *(250)*, HCV RNA assays with a LoD of around 1000 IU/ml would identify at least 95% of viraemic infections *(271)*. A similar analysis has now been undertaken to establish the LoD for HCV RNA assays as test of cure. The multi-cohort analysis comprised 5973 cases of detectable viraemia following HCV treatment in nine countries. (three countries, Egypt *(3264)*, the USA *(1125)* and Georgia *(1041)*, accounted for 80% of cases) and two large clinical trial registries. There was a higher HCV RNA distribution among cases from clinical trials than those from observational databases. In the former, 95% had an HCV RNA greater than 4030 IU/mL (95% CI: 244100) in the clinical trial data as compared with 214 IU/mL (95% CI: 166–266) with the observational studies, while 97% had greater than 923 IU/mL (95% CI: 244030) versus 70 IU/mL (95% CI: 48–86). In another analysis, involving 34 phase 2/3 clinical trials with 330 treatment failure patients *(272)*, 97% had an HCV RNA level greater than 10 000 IU/mL 12 weeks post-treatment, and only 0.9% had a HCV RNA level less than 1000 IU/mL. The consensus is that 95% persons with detectable viraemia at the SVR12 time point are above 1000 IU/mL. Therefore, technologies that can detect viral HCV RNA levels down to 1000 IU/mL would be sufficient for appropriate clinical decision-making in the vast majority of individuals.

[1] Morgan JR, Marsh E, Savinkina A, Shilton S, Shadaker S, Tsertsvadze T, Kamkamidze G, Alkhazashvili M, Morgan T, Belperio P, Backus L, Doss W, Esmat G, Hassany M, Elsharkawy A, Elakel W, Mehrez M, Foster GR, Wose Kinge C, Chew KW, Chasela CS, Sanne IM, Thanung YM, Loarec A, Aslam K, Balkan S, Easterbrook PJ, Linas BP. Determining the lower limit of detection required for HCV viral load assay for test of cure following direct-acting antiviral-based treatment regimens: Evidence from a global data set. J Viral Hepat. 2022 Jun;29(6):474-486. doi: 10.1111/jvh.13672. Epub 2022 Mar 30. PMID: 35278339; PMCID: PMC9248016.

9.3.1 Assessment of HCV RNA POC assays and HCV cAg as a test of cure

No studies were identified that examined the use of POC HCV RNA NAT assays as test of cure.

The LoD of HCV RNA NAT POC assays are 10 IU/mL for GeneXpert using venous blood *(251, 252)* or 100 IU/mL using fingerstick capillary blood. The reported LoD for Genedrive instrument is 2362 IU/mL *(253)*.

The reported LoD for core antigen assay is 1000–3000 IU/mL. The accuracy of HCV cAg for treatment monitoring and to confirm successful viral clearance (test of cure) was assessed by descriptive analysis of five studies *(273-277)* of two HCV cAg assays in comparison with HCV RNA NAT (qualitative and/or quantitative). All studies involved patients with mainly genotype 1b infection and on interferon-based therapy. SVR was assessed in only two studies, with 100% sensitivity and with specificity ranging from 94% to 100%. There were only three studies that evaluated the same assay – the Abbott ARCHITECT HCV Ag assay. There were no studies that evaluated the use of HCV cAg assay for monitoring response to DAA treatment regimens.

9.4 Rationale for the recommendations

9.4.1 Balance of benefits and harms

Use of qualitative or quantitative HCV RNA as a test of cure – existing recommendation

The Guidelines Development Group recommended the use of either qualitative or quantitative NAT detection of HCV RNA as a test of cure at 12 weeks after completion of treatment (or at 24 weeks if 12 weeks is not possible). These assays have a broad dynamic range, from 12 to 7 700 000 IU/mL. All the WHO prequalified laboratory-based quantitative HCV PCR assays have an LoD under 20 IU/mL (and the reviews showed analytical sensitivity as low as 5 IU/mL for qualitative HCV RNA detection by NAT) and would, therefore, capture 99% of individuals with treatment failure. The reviews also showed analytical sensitivity as low as 5 IU/mL for qualitative HCV RNA by NAT. Although either assay was recommended, the lower cost of qualitative assays for HCV RNA makes them preferable to quantitative NAT as a test of cure at 12 weeks *(278-281)*.

Use of POC HCV RNA NAT – new recommendation

The Guidelines Development Group recognized that dependence on detection of HCV RNA by laboratory-based NAT to assess response to HCV antiviral treatment and test of cure, especially in remote settings, could be a barrier to setting up hepatitis C treatment and testing services. The LoD of HCV RNA POC assays are 10 IU/mL for GeneXpert using venous blood *(251, 252)* and 100 IU/mL using fingerstick capillary blood *(282)*. This assay can also accommodate DBS specimens with a detection rate similar to that of fingerstick blood, although the manufacturer does not report an LoD specifically for this approach *(283)*. The Genedrive instrument has reported an LoD of 2362 IU/mL *(253)* and, therefore, might miss some cases of treatment failure. The Guidelines Development Group recommended the use of POC HCV RNA NAT assays as a test of cure that have LoD comparable to laboratory-based assays.

Use of HCVcAg as a test of cure – existing recommendation

The LoD for core antigen assay is 1000–3000 IU/ml. The data on HCVcAg in treatment monitoring and assessment of test of cure (SVR) was considered too limited to recommend its use as a substitute for HCV RNA NAT as a test of cure at SVR12.

9.4.2 Feasibility

In the values and preferences survey, HCV cAg assay was reported as not available at any of the sites, and 40% of respondents also reported that they did not have access to HCV NAT in their countries. The increasing availability of validated POC NAT assays and further reduction in costs of both qualitative and quantitative NAT will be critical to improve access to diagnosis and monitoring in LMICs.

9.5 Implementation considerations

1. **Timing of test of cure**. A test of cure at 24 weeks (SVR24) after completion of treatment may be considered as an alternative SVR time-point if SVR12 is not possible. Similarly, in populations for which there are limited data on the correlation between SVR12 and SVR24 – for example, patients with cirrhosis, HIV/HCV coinfection and other immunocompromised states – SVR24 may be considered.
2. Training, service and maintenance are considerations for both laboratory-based and POC technologies.

9.6 Research gaps

- The kinetics of HCV cAg with DAA treatment should be evaluated, and an optimal time point identified to test with HCVcAg for cure with DAA regimens.
- The correlation between SVR12 and SVR24 should be evaluated in populations where there are limited data, for example, patients with cirrhosis, HIV/HCV coinfection and other immunocompromised states.
- Further studies are needed in different settings and populations to establish the frequency, severity and predictors of HBV reactivation during or after DAA therapy in HBV/HCV coinfected patients.
- The evolution of HCV RNA in patients with viremia >15 IU/mL and <1000 IU/mL 12 weeks following completion of treatment needs further study.

CHAPTER 10. LABORATORY-BASED REFLEX TESTING AND REFLEX SAMPLE COLLECTION FOR HCV VIRAEMIA

10.1 New recommendation on reflex HCV RNA 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 NAT 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 quality of evidence)*

10.2 Background

A key barrier to HCV treatment following a positive HCV antibody test result remains lack of access to an HCV RNA test to confirm active viraemic HCV infection and need for treatment. As a result, a significant proportion never confirm their diagnoses or link to subsequent care and treatment *(284-286)*. One potential way to accelerate access to HCV RNA testing is by implementing reflex testing. We define reflex testing as a linked HCV RNA (or HCVAg) test that is triggered among all people who have an initial positive HCV antibody screening test. Reflex HCV RNA testing may be implemented in two ways: either laboratory-based reflex testing or clinic-based reflex testing.

- **Laboratory-based HCV reflex testing** refers to a testing algorithm in which patients have only a single clinical encounter and one blood draw or specimen for an initial laboratory-based HCV antibody test (in some cases it may be divided in two tubes), which is then sent to the lab. If the sample for HCV antibody testing in the lab is positive, then the same existing or a duplicate specimen is automatically used for a prompt “reflex” laboratory-based HCV RNA NAT or HCVAg) test. The result returned to the patient/doctor is, therefore, for both the HCV antibody result and, if positive, the HCV RNA result. No further visit or specimen collection is required.

- **Clinic-based reflex testing** refers to a testing strategy where there is only a single clinical encounter/visit for an initial rapid diagnostic HCV antibody test, but with two blood draws. A capillary (fingerstick) whole blood specimen is first taken and tested using a rapid diagnostic HCV antibody test, which, if positive (after usually a 15-minute wait), is then immediately followed by a "reflex" second blood specimen collection (either venous blood sample or fingerstick) for HCV RNA detection of current infection. The second blood sample for HCV RNA testing may either be sent to a laboratory for HCV RNA NAT (or HCVAg) test or tested onsite using a point-of-care HCV RNA NAT assay.

Potential advantages of either laboratory or clinic-based reflex testing are improved outcomes across the HCV continuum of care, with increased uptake and reduced time to HCV RNA testing, increased linkage to care, increased uptake and reduced time to treatment. It also eliminates the time, inconvenience and cost of additional clinic visits. Clinic-based reflex sample collection may be further facilitated by access to POC HCV RNA NAT assays.

10.3 Summary of the evidence (Web Annex C)

A WHO-commissioned systematic review and meta-analysis evaluated how much laboratory-based and clinic-based reflex HCV RNA testing reduced turnaround time between HCV antibody screening and HCV RNA testing, linkage to care and treatment when compared with the standard multi-step approach for HCV RNA testing. A total of 51 studies were included, of which nine (17.7%) were from LMICs, and 42 (82.3%) studies were from HICs. We categorized and analysed separately laboratory-based reflex testing (a single clinic encounter and blood specimen, and use of an existing lab specimen for HCV RNA testing) and clinic-based reflex sample collection testing (a single clinical encounter with two specimen collections). 32 studies (62.7%) were categorized as using laboratory-based reflex testing and 19 (37.3%) as using clinic-based reflex testing. Nine of the 32 laboratory-based reflex testing studies also had a non-reflex comparator arm, while none of the clinic-based reflex testing had a comparator arm.

Risk of bias: All of the included studies were either cross-sectional or cohort studies; none was an RTC. Twenty-six studies were assessed as having a high risk of bias, 11 had a moderate risk of bias, and 14 had a low risk of bias. Most of the studies (42 of 51) were published since 2018.

10.3.1 Laboratory-based reflex testing

Uptake of HCV RNA testing, linkage to care and treatment initiation: Overall, 95.7% (95% CI: 92.1–98.3%) of those HCV antibody-positive had an HCV RNA NAT test using laboratory-based reflex testing, and 77.3% (71.3–82.8%) of those testing positive were linked to care. In studies of laboratory-based reflex testing versus non-reflex laboratory-based testing, reflex testing significantly increased the uptake of HCV RNA NAT testing among those testing HCV antibody-positive (pooled RR of 1.35 (95%CI: 1.16–1.58) (based on nine studies, I^2- =99.1%, evidence level: low) and improved linkage to care (pooled RR of 1.47 (95% CI: 0.81–2.67) (based on five studies, I^2- =99.5%, evidence level: very low). Only four studies examined the impact of laboratory-based reflex testing on HCV treatment initiation, and heterogeneity of outcome was large (pooled RR is 1.03 (95% CI: 0.46–2.32) (based on four studies, I^2- =99.3%, evidence level: very low).

Turnaround time: By definition, the turnaround time from antibody test to sampling for reflex testing (either laboratory or clinic-based) was 0 days. Overall, three studies reported the turnaround time from sample collection to HCV RNA testing (21 days, seven days, and 1.6–2.3 days); and seven studies reported the turnaround time from RNA test to treatment initiation among HCV viraemic cases (range 52 to 83 days). The longer turnaround time with some studies was mainly due to batch testing in a lab with low numbers requiring testing, ie waiting for sufficient samples to justify undertaking running an assay.

Survey of key public and private laboratories on laboratory-based reflex HCV RNA testing

Key laboratory networks and referrals, public and private laboratories and national programmes were invited to respond to a web-based survey on their experiences implementing laboratory-based HCV reflex testing. In addition, semi-structured interviews were conducted with laboratory representatives. Five laboratories and associated programmes participated in the development of the case studies; these were Valld'Hebron Clinical Laboratories (VHCL), Barcelona, Spain; United States Veterans Administration – Northeast Ohio Healthcare System; British Columbia Centre for Disease Control Public Health Laboratory (BCCDC PHL); Public Health England, United Kingdom; Mayo Clinic Laboratories, United States. The survey covered at least six operational aspects of laboratory-based reflex testing for HCV infection: *(1)* reasons for initiating laboratory-based reflex testing; *(2)* clinical process for collecting specimens; *()* laboratory protocol for testing specimens; *(4)* costs of implementation; *(5)* acceptability for laboratory staff, clinicians and patients; and *(6)* impact of reflex testing on linkage to care. The findings of the survey informed the implementation considerations reported in section 10.5 and boxes 10.1–10.3.

10.3.2 Clinic-based reflex sampling and testing

Uptake of HCV RNA testing, linkage to care and treatment initiation: In the clinic-based reflex sampling/testing studies, 93.7% (85.1–99.0%) of HCV antibody-positive persons had HCV RNA NAT testing; 74.8% (27.7–100%) were linked to care, and 83.4% (79.2–87.2%) initiated HCV treatment. None of the clinic-based reflex testing studies had a non-reflex comparator arm.

Turnaround time for clinic-based reflex testing: Overall, 13 studies reported the turnaround time from RNA sample collection to HCV RNA NAT testing. The median turnaround time was 0 days in 10 of these studies, one day for two studies and five days for one study. Overall, 12 studies reported a turnaround time from HCV RNA test to available results. Of these, nine reported one day or less, and three studies reported a turnaround time ranging from 6.8 to 8.9 days.

10.4 Rationale for the recommendations

10.4.1 Balance of benefits and harms

The Guideline Development Group made a conditional recommendation for the adoption of HCV RNA reflex testing (either laboratory-based or clinic-based) as an additional strategy to promote uptake of HCV RNA testing following a positive HCV antibody test result and so to promote linkage to care and treatment initiation. This recommendation was based on evidence of low certainty that reflex testing significantly increased the uptake of HCV RNA testing. There was also a non-significant increase in linkage to care and some evidence of reduced turnaround time to treatment initiation with laboratory-based and clinic-based reflex testing, compared with routine non-reflex testing strategies (Web Annex B). Laboratory-based reflex HCV viral load testing is already performed routinely in many laboratory services in high income countries. Clinic-based reflex testing following a positive HCV antibody RDT is also common practice now in low-income countries. Based on the programme survey and costing analysis reported by Public Health England, laboratory-based reflex testing is potentially cost-saving, feasible to implement and has the potential for wide adoption, even in resource-limited settings, to promote HCV testing and treatment uptake. Laboratory-based reflex testing also avoids the need for additional venepuncture and blood draws, which maybe particularly preferred by persons who inject drugs, who are more likely to have compromised veins *(287)*.

10.4.2 Costing and cost–effectiveness

All respondents to the laboratory-based reflex case survey reported that reflex testing was cost-saving compared with conventional two-step testing, even in the absence of formal economic evaluations. Savings were the result of reduced numbers of clinic visits and clinician time. In a 2013 analysis by Public Health England of their laboratory-based reflex testing experience, the estimated annual savings gained from reflex RNA NAT testing of an anti-HCV positive sample was £166 500, due to the reduction in the number of persons being referred from 6001 in the non-reflex pathway to 3781 in the reflex pathway. Since these cost savings did not include the additional cost of referral to treatment in the non-reflex pathway, the total savings are likely to be even higher. There is potential for further savings, as one specimen could be used to test for multiple pathogens, such as HBV and HIV, on high-throughput laboratory machines *(288, 289)*.

10.4.3 Values and preferences (Web Annex D)

In a multi-country online survey of 210 people in 49 countries undertaken by the World Hepatitis Alliance and Coalition Plus, 88% of participants confirmed a strong preference to "do your initial and confirmatory HCV RNA tests on the same day". This level of preference was even higher, at 96%, among people who currently inject drugs and who formerly injected drugs. The main reasons given were the possibility to more quickly confirm diagnosis (81%) and start treatment (76%). There was also a strong preference, from 93% of respondents, for doing both the initial screening test and confirmatory HCV RNA NAT testing at the same place, for convenience (70%), and at a community-friendly site (60%). A further consideration in favour of HCV reflex testing is that, as noted, persons who inject drugs may prefer a testing strategy that requires only one standard venepuncture *(287)* .

10.4.4 Equity

Overall, strategies to promote uptake and linkage to care, such as laboratory or clinic-based reflex testing, will likely further promote equity in access if used in settings and populations at high risk of loss to follow-up, who benefit from the convenience of a single sample collection approach, such as the homeless and people who inject drugs at harm reduction sites and people in prisons.

10.4.5 Feasibility

There are multiple examples, mainly in high income countries, of the feasibility of routine laboratory-based reflex HCV RNA NAT testing. The experiences of three laboratories are presented as case studies in boxes 10.1–10.3. Our findings also support the feasibility of implementing clinic-based reflex testing. The systematic review included 19 studies that used HCV RNA reflex testing in POC or near POC settings (that is, HCV clinics and drug treatment sites) and did not send samples to a laboratory for confirmation testing. Compared with standard laboratory-based HCV RNA testing, reflex testing or one-time sample collection simplified the care pathway and reduced the need for additional clinic visits and time to POC HCV RNA NAT test and linkage to care.

10.5 Implementation considerations

Adaptation of reflex HCV RNA testing recommendations for different country contexts

Countries should incorporate routine reflex HCV RNA testing into their national testing guidelines and testing infrastructure. The choice between laboratory-based reflex testing and clinic-based reflex testing with POC HCV RNA tests will depend on national testing policies, budgets, infrastructure and human resources, as well as the extent of reliance on centralized high-throughput laboratories, the available sample transport network and location of testing and treatment services.

While a laboratory-based reflex testing strategy will be more appropriate in settings with large testing volumes supported by extensive sample transport networks, clinic-based reflex sample collection for HCV RNA testing may be the preferred testing algorithm for populations such as key populations (such as people who inject drugs and men who have sex with men) and migrants and refugees who receive health care in community-based settings or in primary care and may have limited access to full-range phlebotomy and laboratory services. Instead, clinic-based reflex testing with initial HCV antibody RDTs followed by reflex sample collection for HCV RNA testing of those testing antibody-positive and then use of clinic-based POC HCV RNA testing may maximize linkage to care for such populations. To meet the needs of different populations or regions in a country, a mix of clinic-based and laboratory-based reflex testing strategies may be optimal.

Key steps to initiate laboratory-based reflex HCV RNA testing

- Train outpatient clinic phlebotomy and laboratory staff on new procedures for specimen collection and processing of HCV RNA NAT testing.
- Update electronic laboratory order forms for anti-HCV and RNA testing to list reflex-only testing options and develop laboratory guidance for HCV reflex testing.
- Design the laboratory process to preserve specimen integrity and limit risk of cross-contamination.
- Plan for additional costs as needed, that is, additional tubes, transport and storage, if collecting two tubes for anti-HCV and NAT/cAg testing.
- Combine laboratory-based reflex HCV RNA NAT testing with other strategies, for example, clinic-based reflex testing, to meet the needs of different populations.
- Evaluate HCV laboratory-based reflex testing programmes, providing feedback to providers and laboratory managers for quality improvement.

Other operational considerations

- **Training for phlebotomists will be required to sensitize new protocols:** If the reflex testing protocol requires two separate specimen tubes and phlebotomists are used to only collecting one specimen tube for HCV testing, appropriate training and quality management assurance systems are needed to sensitize phlebotomists to collecting two tubes and using two tube labels.
- **Electronic ordering system updates must be comprehensive to disable all non-reflex testing options.** Electronic ordering systems are not necessary for reflex testing, but they can help streamline the transition to a new clinical process.
- **Designing the clinical process to collect one versus two specimens may depend on the assessed risk of contamination in the laboratory.** Laboratory managers should assess the risk of cross-contamination for available testing platforms and develop procedures to minimize this risk.

BOX 10.1 Case study: HCV reflex testing in Valld'Hebron Clinical Laboratories, Barcelona, Spain

Setting

Valld'Hebron Clinical Laboratories (VHCL) serves Valld'Hebron University Hospital, a facility with 1200 beds and 11 000 employees and also 116 primary care and Drug Addiction Care and Monitoring Centres in Barcelona. VHCL serves about 6000 patients per day, running 25 000 specimens per day, for a total of about 20 million tests per year.

Previous testing protocol

Between January 2017 to February 2018, only 52% (n=1412/2176) of positive HCV antibody tests resulted in a request for viral load HCV RNA testing in the primary care clinics *(290)*. The percentage was even lower in the drug addiction care centres. The conventional testing strategyalgorithm required five visits to receive a confirmatory diagnosis, which could take at least four weeks. In the report of a positive anti-HCV test returned to the clinician, the laboratory promoted the ordering of an HCV viral load HCV RNA test for patients who tested positive for HCV antibody. However, this strategy proved ineffective to increase the uptake of viral load HCV RNA testing.

Initiation of reflex testing

In March 2018, as recommended by the European Association for the Study of the Liver (EASL), Valld'Hebron implemented reflex testing.

Clinical process

Valld'Hebron implemented a one-step testing process that involved collecting two specimens at the initial clinic visit. This reduced the time from specimen collection to HCV diagnosis from four weeks to about two days. The first specimen collected by the phlebotomist was a serum sample for HCV antibody testing. The second specimen was plasma with EDTA used for blood count determination. In patients with first specimens that tested positive for HCV antibody, the second specimen was also used to test for HCV RNA. Results of HCV RNA testing were provided within 24 hours after the positive HCV antibody test result Monday through Thursday, and within three days if the antibody test was performed on a Friday. In some settings under the Valld'Hebron University Hospital umbrella, DBS and plasma separation cards were used to collect samples from patients.

Laboratory protocol

Serological testing (for HCV antibody) was performed on the Cobas 8000 platform (Roche Molecular Systems, USA) with single-use (that is, disposable) tips. The second specimen for reflex HCV RNA testing was processed unopened (flow cytometry). Determination of HCV

RNA was performed with a Cobas 6800 analyser (Roche Molecular Systems, USA). The blood count analysis prior to determination of HCV RNA was performed by flow cytometry with a Sysmex XN-20 analyser (Sysmex Corporation, Japan). This protocol was possible because the Sysmex XN-20 analyser can perform hematimetric measures without de-capping blood tubes. (The rubber cap is punctured by a needle.)

Valld'Hebron ruled out the use of one specimen for both serological and virologic testing due to the assessment of a high-risk for contamination across serological and virologic testing. Because the Roche Cobas 6800 analyser used for serological testing centralizes serological determinations, the system tends to concentrate specimens with serologic evidence of HCV infection (that is, potentially anti-HCV positive). Although the Cobas 8000 analyser uses disposable tips, specimens reach the analytical system uncapped and, therefore, are vulnerable to environmental aerosols and occasional hand manipulations, which may increase the risk of contamination. As a precautionary measure, the laboratory decided that the serological specimens should not be used for virologic determination. By comparison, all blood count determinations are randomly processed (more than 5000 a day), meaning that potential anti-HCV-positive cases (about five to 10 a day) would be randomly distributed among these 5000 samples, statistically reducing the probability of cross-contamination associated with that of two anti-HCV-positive cases being next to each other, where one positive HCV RNA specimen could contaminate a nearby negative HCV RNA sample.

Impact of HCV reflex testing

Based on a comparison of the conventional, non-reflex testing protocol from January 2017 to February 2018 with the reflex testing protocol implemented from March 2018 to December 2018, HCV RNA NAT reflex testing improved the proportion of persons with positive antibody tests who received HCV RNA NAT testing from 61.5% (n=910/1480) to 92.1% (n=1772/1924) in primary care settings. In drug addiction care and monitoring centres, the proportion of persons with positive antibody tests linked to RNA NAT testing improved from 77.3% (n=133/172) to 95.1% (n=233/245) *(290)*.

Note on cost implications

No formal economic analysis has been done to compare the cost of HCV reflex testing in the Valld'Hebron laboratory network with conventional two-step testing strategy algorithms. Still, laboratory representatives have noted that the cost of a viral RNA determination (less than € 30) is much less than the cost of a second physician appointment and blood collection.

BOX 10.2 Case study: British Columbia Centre for Disease Control Public Health Laboratory (BCCDC PHL)

Setting

The British Columbia Centre for Disease Control Public Health Laboratory (BCCDC PHL) is the primary public health and reference diagnostic testing facility for the province of British Columbia, Canada.

Previous testing protocol

At the end of 2019, analyses of the British Columbia (BC) Hepatitis Testers Cohort (HTC) found that approximately 16% of people in BC who had tested HCV antibody positive, and were alive and living in BC, had never had an HCV RNA NAT test (n=8491 people as of end of 2019) *(291)*. Introducing automated HCV RNA NAT reflex testing was proposed to address this gap in assessment for active HCV infection following positive screening results. This improvement in HCV virologic testing could also facilitate better progress along the HCV care cascade, by reducing visits for patients, reducing the number of blood collections and potentially reducing physicians' workload.

Initiation of reflex testing

HCV laboratory-based reflex testing was introduced in January 2020. The main start-up investments to implement HCV NAT reflex testing were developing laboratory standard operating procedures and mapping process changes. Training for laboratory staff and clinicians was required. No capital investments were required.

Four main challenges were overcome:

1. validation of performance of serum specimens on HCV RNA NAT assay and ensuring that there was a process to request a follow-up ethylenediamine tetraacetic acid (EDTA) **venous whole blood specimen** if there were concerns regarding false negative HCV RNA NAT results due to serum-related specimen integrity concerns
2. revision of laboratory testing and resulting workflows, including laboratory information system updates
3. training laboratory staff and development of job aids and standard operating procedures for implementation
4. educating clinicians on the fact that, if patients have had a previous HCV RNA NAT assay, they will not be picked up in the HCV RNA reflex pathway from an anti-HCV test.

Clinical process

All clinical settings in the laboratory network, both in-patient and out-patient, are eligible for reflex testing. HCV RNA NAT results from a reflexed test are reported to the ordering

provider, who is then responsible for returning all results to the patient. The HCV RNA NAT results from a reflexed test are reported separately from the initial anti-HCV results (that is, two separate result reports are sent), but results are viewable on the patient's electronic testing record. The typical turn-around time between specimen receipt and return of test results is five days (BCCDC PHL medically accepted standard).

Laboratory protocol

Serum specimens are received and accessioned for test requested (that is, anti-HCV) in the Laboratory Information System. Serum specimens are stored in a refrigerator at 4 °C prior to being sent for anti-HCV screening on the Siemens Centaur XP System analyser (Siemens Healthineers, USA). Anti-HCV screening using primary serum tubes on the Siemens Centaur does not result in carryover because individual pipets are used. If the anti-HCV screen is positive, the specimen then undergoes supplemental testing for anti-HCV on the Abbott ARCHITECT HCV Ag analyser (DENKA SEIKEN CO., LTD., Japan for Abbott GmbH & Co. KG, Germany). If the result of supplemental testing is positive for anti-HCV and the screen index value was >11 on the Siemens Centaur XP Centaur, then the technician looks up that patient's previous HCV testing history. If the patient is a new anti-HCV positive or has never previously had an HCV RNA NAT test performed at the lab, then the HCV RNA NAT (reflex) test is accessioned, and the specimen is sent for the HCV RNA NAT test.

The HCV RNA NAT testing is conducted using either the Abbott m2000 or Abbott ALLINITY platforms. If an EDTA plasma specimen was collected from that patient at the same time as the serum specimen and there is specimen left, that will preferentially be used for the HCV NAT, however, if EDTA plasma is not available, the original serum specimen that was used for anti-HCV test will be used. If serum was used for testing and HCV RNA is not detected, a follow-up EDTA blood HCV RNA test is requested to minimize the risk of a false negative HCV RNA result due to concerns about serum sample integrity. The storage time limit for virologic testing of samples is 14 days. After testing, any remnant anti-HCV or HCV RNA positive specimens are aliquoted and stored indefinitely at –20 oC. Reflex testing is conducted as specimens arrive.

Economic considerations

On average a consultation with a family physician is billed at CA$ 91.94. Therefore, for two separate visits (standard HCV testing algorithm), the total cost to the payer would be CA$ 194.76, whereas, for only one visit (HCV RNA reflex testing algorithm), it would cost the payer only CA$ 97.38. This calculation does not include cost-savings to the patient such as savings on transportation and less time off work to attend appointments.

BOX 10.3 Case study: HCV reflex testing in Public Health England

Initiation of reflex testing

The 2012 UK Public Health Guidelines on HCV testing from the National Institute for Health and Care Excellence (NICE) state that commissioners should ensure that laboratories automatically test anti-HCV positive specimen for the presence of HCV RNA (reflex testing) or else refer the specimen to a laboratory that can perform this test *(292)*. However, as an RNA test is more expensive than an anti-HCV test, individual laboratory contracts at the time prohibited automatic RNA testing unless there was a specific clinical request. A study by Public Health England in 2013 *(293)* found that between 2008 and 2013, before the recommendation of reflex testing, only 53% of positive anti-HCV specimen were subjected to routine viral load HCV RNA NAT testing. Rates of HCV reflex testing varied by laboratory, ranging from 21.2% to 94.4% of anti-HCV positive specimens. Compared with general practitioner services, reflex testing was more likely to occur in specialist liver services (OR 3.4; 95% CI: 3.0–3.8), prisons (OR 2.3; 95% CI: 2.1–2.6), drug treatment centres (OR 2.3; 95% CI: 2.1–2.5) and specialist HIV services (OR 1.86; 95% CI: 1.43–2.40). Separation of the service arrangements for HCV-testing and care, with multiple organizations involved (including Local Authorities, Clinical Commissioning Groups and National Health Service England), limited widespread implementation.

Laboratory protocol

One whole-blood EDTA venous whole blood specimen is collected for anti-HCV testing and HCV RNA NAT testing of HCV antibody positive specimens. Specimens are transported and processed as soon as possible. If processing is delayed, refrigeration is preferable to storage at ambient temperature. Specimens for HCV RNA NAT can be stored long-term at –20° or –70°C to minimize RNA loss. Samples are retained in accordance with the Royal College of Pathologists guidelines, The retention and storage of pathological records and specimens *(294)*.

Economic considerations

In the 2013 Public Health England analysis, the estimated annual savings gained from automatic RNA testing of an anti-HCV positive specimen was £166 500, attributable to a reduction in the number of persons being referred from 6001 in the non-reflex pathway to 3781 in the reflex pathway. This calculation does not include the additional referral cost to treatment in the non-reflex pathway.

Impact

Public Health England found that patients diagnosed via reflex testing received treatment more quickly than those who were RNA NAT tested between one week and six months later (average 167.5 days versus 282.5 days, $p<0.0001$).

TABLE 10.1 Comparative costs of non-reflex and reflex testing pathways for Public Health England HCV testing programme

Non-reflex pathway	Unit cost (£)	Number of persons	Total cost (£)
Anti-HCV test	7.4	236 185	1 747 769
Referral of anti-HCV positives	75	6001	450 075
HCV RNA test	64.2	6001	385 264
Total			2 583 108
Reflex pathway			
Anti-HCV test	7.4	236 185	1 747 769
HCV RNA test on anti-HCV positives	64.2	6001	385 264
Referral of HCV RNA positives	75	3781	283 575
Total			2 416 608

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