



NOVEMBER 2016
**GUIDELINES ON
HEPATITIS B AND C TESTING**

POLICY BRIEF

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BACKGROUND

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are major causes of chronic liver disease (including cirrhosis and hepatocellular carcinoma), and worldwide cause an estimated 1.4 million deaths annually. It is estimated that 240 million people are living with chronic HBV infection, and that 110 million persons are HCV antibody positive, of which 80 million have viraemic infection. The burden of HBV and HCV remains disproportionately high in low- and middle-income countries (LMICs), particularly in Asia and Africa. Additionally, even in low-prevalence areas, certain populations have high levels of HCV and HBV infection, such as persons who inject drugs (PWID), men who have sex with men (MSM), HIV-infected individuals, as well as some indigenous communities.

The development of highly effective, well-tolerated oral treatment regimens with high rates of cure after 12 weeks of treatment has revolutionized the treatment of chronic HCV infection, although the high prices of these new medicines remain a major barrier to access in many countries. Effective long-term antiviral treatment with tenofovir or entecavir is also available for people with chronic HBV infection.

Despite the high global burden of disease due to HBV and HCV infection, and the advances and opportunities for treatment, the majority of people infected with HBV or HCV remain unaware of their infection and therefore frequently present with advanced disease. There are several key reasons for this very low rate of hepatitis testing. These include limited facilities or services for hepatitis testing, lack of national testing policies or guidelines, costly and complex diagnostic assays and algorithms, and poor laboratory capacity and quality assurance systems.

Testing and diagnosis of chronic HBV and HCV infection is the gateway for access to both prevention as well as care and treatment services. Early identification of persons with chronic HBV or HCV infection enables them to receive the necessary care and treatment to prevent or delay progression of liver disease. Testing also provides an opportunity to link to interventions to reduce transmission, through counselling on risk behaviours and provision of prevention commodities (such as sterile needles and syringes) and hepatitis B vaccination.

ABOUT THE GUIDELINES

These are the first WHO guidelines on testing for chronic HBV and HCV infection and complement published guidance by WHO on the prevention, care and treatment of chronic HCV¹ and HBV² infection. These guidelines outline the public health approach to strengthening and expanding current testing practices for HBV and HCV infection, and are intended for use across age groups and populations. The primary audience for these guidelines are national programme managers in ministries of health and health-care providers in LMICs responsible for planning and implementing hepatitis testing, prevention, care and treatment services.

The guidelines are organized into three distinct sections:

Introduction:

Introductory contents on epidemiology, natural history and in vitro diagnostic assays for hepatitis B and C virus infection.

Recommendations:

Summary of recommendations, evidence and rationale.

Implementation:

Guidance to support implementation of these recommendations at country level.

¹ Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection. Updated version, April 2016. Geneva: World Health Organization; 2016.

² Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015.

RECOMMENDATIONS



Table 1 summarises the recommendations on who to test and testing approaches; how to test and testing strategies; and interventions to promote uptake of testing and linkage to care.

Who to test for HBV and HCV infection - testing approaches

The guidelines recommend to offer focused testing to individuals from populations most affected by HBV or HCV infection (i.e. who are either part of a population with higher seroprevalence or who have a history of exposure or high-risk behaviours for HBV or HCV infection). In settings with a $\geq 2\%$ or $\geq 5\%$ seroprevalence of hepatitis B surface antigen (HBsAg) or HCV antibody (anti-HCV), it is recommended that all adults have routine access and be offered testing (i.e. a general population testing approach), or use “birth cohort” testing for specific age groups with higher anti-HCV seroprevalence. These different testing approaches should make use of existing facility-based (such as antenatal clinics, HIV or TB services) or community-based testing opportunities and programmes.

How to test for HBV and HCV infection - serological assays and testing strategies

Overall, the guidelines recommend the use of a single quality-assured serological in vitro diagnostic test (IVD) (i.e. either a laboratory-based immunoassay (enzyme immunoassay or chemiluminescence immunoassay) or rapid diagnostic test [RDT]) to detect HBsAg and HCV antibody. RDTs used should meet minimum performance standards, and be delivered at the point of care to improve access and linkage to care and treatment.

Confirming viraemic infection and monitoring for treatment response

Following a reactive HCV antibody serological test result, a quantitative or qualitative RNA nucleic acid test (NAT) is recommended as the preferred testing strategy to diagnose viraemic infection. Detection of core HCV antigen, where the assay has comparable clinical sensitivity to NAT technologies, may be considered as an alternative. The use of HBV DNA NAT following a reactive HBsAg serological test result, is recommended to help further guide who to treat or not treat if there is no evidence of cirrhosis, and to monitor for treatment response, based on existing recommendations from the 2015 WHO HBV management guidelines.

Use of dried blood spot (DBS) and other strategies to promote uptake of testing and linkage to care

The use of capillary whole blood DBS specimen collection for both serological and NAT technologies for HBV and HCV infection may be considered to facilitate access to testing in certain settings where there are either no facilities or expertise to take venous blood specimens, in persons with poor venous access, or where quality-assured RDTs are not available or their use is not feasible. Programmes should consider only the use of assays that have been validated by their manufacturer for use with DBS specimens. Other recommended interventions to promote uptake of hepatitis testing and linkage to care include peer and lay health worker support in community-based settings, clinician reminders in facilities, and testing as part of integrated services within drug treatment and community-based harm reduction services.

The GRADE system (Grading of Recommendations, Assessment, Development and Evaluation) was used to categorise both the strength of recommendations as strong or conditional (based on consideration of the quality of evidence, balance of benefits and harms, acceptability, resource use and programmatic feasibility) and the quality of evidence as high, moderate, low or very low.

IMPLEMENTATION



Implementation of these recommendations pose practical challenges to policy-makers and implementers in LMICs, particularly in sub-Saharan Africa, where there is currently very limited access to diagnostic assays, antiviral therapies and appropriate laboratory infrastructure. These guidelines also provide a framework for country decision-making and

planning in two key areas, summarised in Box below. There is also guidance on different service delivery models for testing, pre and post test counselling, and tailored testing approaches in specific populations (e.g. persons who inject drugs, prisoners, pregnant women, couples and partners, children and adolescents).

How to organise hepatitis laboratory testing services

To ensure the quality and accuracy of hepatitis testing. This includes consideration of the following key elements:

- **A national framework for hepatitis testing** (e.g. national testing policies, regulatory mechanism, and national reference laboratory);
- **Financing strategy and planning;**
- **Building capacity for testing services** (e.g. management of human resources, procurement and supply chain, storage and transportation, equipment and laboratory information systems);
- **Setting national standards for testing** (e.g. performance and operational characteristics for assays, standardized testing strategies, validation of testing algorithms (product selection), and methodology for assay selection);
- **Assuring quality and safety of testing services** (e.g. quality management systems, personnel, training and supportive supervision)

How to plan the best strategic mix of different testing approaches

There are many facility- and community-based approaches to delivering hepatitis testing. Countries need to consider a strategic mix of these different testing approaches to reach different populations and those currently undiagnosed, including opportunities to integrate hepatitis testing with existing services. The selection of testing approaches should be based on consideration of the following:

- **National context and epidemiology** (e.g. prevalence, populations affected and undiagnosed burden);
- **Existing health-care and testing infrastructure** and laboratory specimens testing referral network;
- **Current testing uptake and coverage** (number and proportion with chronic HBV or HCV who have been diagnosed)³;
- **Programme costs and cost-effectiveness** of different testing approaches at national and subnational levels;
- **Available financial and human resources**

The guidelines will provide a major opportunity to improve identification and treatment of persons with chronic HBV and HCV infection, and achieve the 2016 Global Health Sector Strategy (GHSS) on viral Hepatitis⁴ targets on testing (i.e. to identify 30% of

persons living with HBV and HCV infection by 2020 and 90% by 2030) and treatment. This in turn will improve clinical outcomes, save lives, reduce HBV and HCV transmission and prevent new infections.

³ WHO Monitoring and evaluation for viral hepatitis B and C: recommended indicators and framework. Geneva: World Health Organization; 2016

⁴ WHO Global health sector strategy on viral hepatitis 2016-2021. Geneva: World Health Organization; 2016.

TABLE 1 WHO RECOMMENDATIONS ON TESTING FOR CHRONIC HEPATITIS B AND C VIRUS INFECTION

WHO TO TEST FOR CHRONIC HBV INFECTION	
Testing approach and population	Recommendations*
General population testing	<p>1. In settings with a $\geq 2\%$ or $\geq 5\%$¹ HBsAg seroprevalence in the general population, it is recommended that all adults have routine access to and be offered HBsAg serological testing with linkage to prevention, care and treatment services.</p> <p>General population testing approaches should make use of existing community- or health facility-based testing opportunities or programmes such as at antenatal clinics, HIV or TB clinics.</p> <p><i>Conditional recommendation, low quality of evidence</i></p>
Routine testing in pregnant women	<p>2. In settings with a $\geq 2\%$ or $\geq 5\%$¹ HBsAg seroprevalence in the general population, it is recommended that HBsAg serological testing be routinely offered to all pregnant women in antenatal clinics², with linkage to prevention, care and treatment services. Couples and partners in antenatal care settings should be offered HBV testing services.</p> <p><i>Strong recommendation, low quality of evidence</i></p>
Focused testing in most affected populations	<p>3. In all settings (and regardless of whether delivered through facility- or community-based testing), it is recommended that HBsAg serological testing and linkage to care and treatment services) be offered to the following individuals:</p> <ul style="list-style-type: none"> • Adults and adolescents from populations most affected by HBV infection³ (i.e. who are either part of a population with high HBV seroprevalence or who have a history of exposures and/or high-risk behaviours for HBV infection); • Adults, adolescents and children with a clinical suspicion of chronic viral hepatitis⁴ (i.e. symptoms, signs, laboratory markers); • Sexual partners, children and other family members, and close household contacts of those with HBV infection⁵; • Health-care workers: in all settings, it is recommended that HBsAg serological testing be offered and hepatitis B vaccination given to all health-care workers who have not been vaccinated previously (<i>Adapted from existing guidance on Hepatitis B vaccination⁶</i>) <p><i>Strong recommendation, low quality of evidence</i></p>
Blood donors <i>Adapted from existing 2010 WHO guidance (Screening donated blood for transfusion transmissible infections⁷)</i>	<p>4. In all settings, screening of blood donors should be mandatory with linkage to care, counselling and treatment for those who test positive.</p>

Abbreviations: HBsAg: Hepatitis B surface antigen; PWID: People who inject drugs; MSM: Men who have sex with men

*The GRADE system (Grading of Recommendations, Assessment, Development and Evaluation) was used to categorise the strength of recommendations as strong or conditional (based on consideration of the quality of evidence, balance of benefits and harms, acceptability, resource use and programmatic feasibility) and the quality of evidence as high, moderate, low or very low.

¹ A threshold of $\geq 2\%$ or $\geq 5\%$ seroprevalence was based on several published thresholds of intermediate or high seroprevalence. The threshold used will depend on other country considerations and epidemiological context.

² Many countries have chosen to adopt routine testing in all pregnant women, regardless of seroprevalence in the general population, and particularly where seroprevalence $\geq 2\%$. A full vaccination schedule including birth dose should be completed in all infants, in accordance with WHO position paper on Hepatitis B vaccines 2009.⁶

³ Includes those who are either part of a population with higher seroprevalence (e.g. some mobile/migrant populations from high/intermediate endemic countries, and certain indigenous populations) or who have a history of exposures or high-risk behaviours for HBV infection (e.g. PWID, people in prisons and other closed settings, MSM and sex workers, HIV-infected persons, partners, family members and children of HBV infected persons).

⁴ Features that may indicate underlying chronic HBV infection include clinical evidence of existing liver disease, such as cirrhosis or hepatocellular carcinoma (HCC), or where there is unexplained liver disease, including abnormal liver function tests or liver ultrasound.

⁵ In all settings, it is recommended that HBsAg serological testing with hepatitis B vaccination of those who are HBsAg negative and not previously vaccinated be offered to all children with parents or siblings diagnosed with HBV infection or with clinical suspicion of hepatitis, through community- or facility-based testing.

⁶ WHO position paper. Hepatitis B vaccines. Weekly epidemiological record. 4 (84):405-420, 2009

⁷ Screening donated blood for transfusion transmissible infections. Geneva: World Health Organization; 2010

WHO TO TEST FOR CHRONIC HCV INFECTION

Testing approach and population	Recommendations*
Focused testing in most affected populations	<p>1. In all settings (and regardless of whether delivered through facility- or community-based testing), it is recommended that serological testing for HCV antibody (anti-HCV)¹ be offered with linkage to prevention, care and treatment services to the following individuals:</p> <ul style="list-style-type: none"> • Adults and adolescents from populations most affected by HCV infection² (ie. who are either part of a population with high HCV seroprevalence or who have a history of exposures and/or high-risk behaviours for HCV infection); • Adults and children with a clinical suspicion of chronic viral hepatitis³ (ie. symptoms, signs, laboratory markers). <p><i>Strong recommendation, low quality of evidence</i></p> <p><i>Note: Periodic re-testing using HCV NAT should be considered for those with ongoing risk of acquisition or reinfection.</i></p>
General population testing	<p>2. In settings with a $\geq 2\%$ or $\geq 5\%$⁴ HCV antibody seroprevalence in the general population it is recommended that all adults have access to and be offered HCV serological testing with linkage to prevention, care and treatment services.</p> <p>General population testing approaches should make use of existing community- or facility-based testing opportunities or programmes such as HIV or TB clinics, drug treatment services and antenatal clinics⁵.</p> <p><i>Conditional recommendation, low quality of evidence</i></p>
Birth cohort testing	<p>3. This approach may be applied to specific identified birth cohorts of older persons at higher risk of infection⁶ and morbidity within populations that have an overall lower general prevalence.</p> <p><i>Conditional recommendation, low quality of evidence</i></p>

Abbreviations: NAT: nucleic acid test; anti-HCV: HCV antibody; PWID: People who inject drugs; MSM: Men who have sex with men

*The GRADE system (Grading of Recommendations, Assessment, Development and Evaluation) was used to categorise the strength of recommendations as strong or conditional (based on consideration of the quality of evidence, balance of benefits and harms, acceptability, resource use and programmatic feasibility) and the quality of evidence as high, moderate, low or very low.

¹ This may include 4th generation combined antibody/antigen assays

² Includes those who are either part of a population with higher seroprevalence (e.g. some mobile/migrant populations from high/intermediate endemic countries, and certain indigenous populations) or who have a history of exposures or high-risk behaviours for HCV infection (e.g. PWID, people in prisons and other closed settings, MSM and sex workers, and HIV-infected persons, children of mothers with chronic HCV infection especially if HIV-coinfected).

³ Features that may indicate underlying chronic HCV infection include clinical evidence of existing liver disease, such as cirrhosis or hepatocellular carcinoma (HCC), or where there is unexplained liver disease, including abnormal liver function tests or liver ultrasound.

⁴ A threshold of $\geq 2\%$ or $\geq 5\%$ seroprevalence was based on several published thresholds of intermediate and high seroprevalence. The threshold used will depend on other country considerations and epidemiological context.

⁵ Routine testing of pregnant women for HCV infection is currently not recommended.

⁶ Because of historical exposure to unscreened or inadequately screened blood products and/or poor injection safety.

HOW TO TEST FOR CHRONIC HBV INFECTION AND MONITOR TREATMENT RESPONSE

Topic	Recommendations*
Which serological assays to use	<ul style="list-style-type: none"> For the diagnosis of chronic HBV infection in adults and children (>12 months of age¹), a serological assay (in either RDT or laboratory-based immunoassay format²) that meets minimum quality, safety and performance standards³ (<i>with regard to both analytical and clinical sensitivity and specificity</i>) is recommended to detect hepatitis B surface antigen (HBsAg). <ul style="list-style-type: none"> In settings where existing laboratory testing is already available and accessible, laboratory-based immunoassays are recommended as the preferred assay format. In settings where there is limited access to laboratory testing and/or in populations where access to rapid testing would facilitate linkage to care and treatment, use of RDTs is recommended to improve access. <p><i>Strong recommendation, low/moderate quality of evidence</i></p>
Serological testing strategies	<ul style="list-style-type: none"> In settings or populations with an HBsAg seroprevalence of $\geq 0.4\%$⁴, a single serological assay for detection of HBsAg is recommended, prior to further evaluation for HBV DNA and staging of liver disease. In settings or populations with a low HBsAg seroprevalence of $< 0.4\%$⁴, confirmation of HBsAg positivity on the same immunoassay with a neutralization step or a second different RDT assay for detection of HBsAg may be considered⁵. <p><i>Conditional recommendation, low quality of evidence</i></p>
Detection of HBV DNA – Assessment for treatment <i>Adapted from existing guidance (WHO HBV 2015 guidelines⁶)</i>	<ul style="list-style-type: none"> Directly following a positive HBsAg serological test, the use of quantitative or qualitative nucleic acid testing (NAT) for detection of HBV DNA is recommended as the preferred strategy and to guide who to treat or not treat. <p><i>Strong recommendation, moderate/low quality of evidence</i></p>
Monitoring for HBV treatment response and disease progression <i>Existing guidance (WHO HBV 2015 guidelines⁶)</i>	<ul style="list-style-type: none"> It is recommended that the following be monitored at least annually: <ul style="list-style-type: none"> ALT levels (and AST for APRI), HBsAg⁷, HBeAg⁸, and HBV DNA levels (where HBV DNA testing is available) Non-invasive tests (APRI score or transient elastography) to assess for presence of cirrhosis in those without cirrhosis at baseline; If on treatment, adherence should be monitored regularly and at each visit. <p><i>Strong recommendation, moderate quality of evidence</i></p> <p>More frequent monitoring is recommended:</p> <ul style="list-style-type: none"> In persons on treatment or following treatment discontinuation: more frequent on-treatment monitoring (at least every 3 months for the first year) is indicated in: persons with more advanced disease (compensated or decompensated cirrhosis⁹); during the first year of treatment to assess treatment response and adherence; where treatment adherence is a concern; in HIV-coinfected persons; and in persons after discontinuation of treatment. <i>Conditional recommendation, very low quality of evidence</i> In persons who do not yet meet the criteria for antiviral therapy: i.e. persons who have intermittently abnormal ALT levels or HBV DNA levels that fluctuate between 2000 IU/mL and 20 000 IU/mL (where HBV DNA testing is available) and in HIV-coinfected persons⁷. <i>Conditional recommendation, low quality of evidence</i>

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; APRI: aspartate-to-platelet ratio index; HBeAg: HBV e antigen; HBsAg: HBV surface antigen; NAT: nucleic acid test; RDT: rapid diagnostic test

¹ A full vaccination schedule including birth dose should be completed in all infants in accordance with WHO position paper on Hepatitis B vaccines, 2009. Testing of exposed infants is problematic within the first six months of life as HBsAg and hepatitis B DNA may be inconsistently detectable in infected infants. Exposed infants should be tested for HBsAg between 6 and 12 months of age to screen for evidence of hepatitis B infection. In all age groups, acute HBV infection can be confirmed by the presence of HBsAg and IgM anti-HBc. CHB is diagnosed if there is persistence of HBsAg for six months or more.

² Laboratory-based immunoassays include enzyme immunoassay (EIA), chemoluminescence immunoassay (CLIA), and electrochemoluminescence assay (ECL).

³ Assays should meet minimum acceptance criteria of either WHO prequalification of IVDs or a stringent regulatory review for IVDs. All IVDs should be used in accordance with manufacturers' instructions for use and where possible at testing sites enrolled in National or International External Quality Assessment Scheme.

⁴ Based on results of predictive modelling of positive predictive values according to different thresholds of seroprevalence in populations to be tested, and assay diagnostic performance.

⁵ A repeat HBsAg assay after 6 months is also a common approach used to confirm chronicity of HBV infection.

⁶ For further details, see See Chapter 5: Who to treat and who not to treat. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection: World Health Organization; 2015.

⁷ In persons on treatment, monitor for HBsAg loss (although this occurs rarely), and for seroreversion to HBsAg positivity after discontinuation of treatment.

⁸ Monitoring of HBeAg/anti-HBe mainly applies to those who are initially HBeAg positive. However, those who have already achieved HBeAg seroconversion and are HBeAg negative and anti-HBe positive may serorevert.

⁹ Decompensated cirrhosis is defined by the development of 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.

HOW TO TEST FOR CHRONIC HCV INFECTION AND MONITOR TREATMENT RESPONSE

Topic	Recommendations*
Which serological assays to use	<ul style="list-style-type: none"> To test for serological evidence of past or present infection in adults and children (>18 months of age¹), an HCV serological assay (antibody or antibody/antigen) using either RDT or laboratory-based immunoassay formats² that meets minimum safety, quality and performance standards³ (<i>with regard to both analytical and clinical sensitivity and specificity</i>) is recommended. <ul style="list-style-type: none"> In settings where there is limited access to laboratory infrastructure and testing, and/or in populations where access to rapid testing would facilitate linkage to care and treatment, RDTs are recommended. <p><i>Strong recommendation, low/moderate quality of evidence</i></p>
Serological testing strategies	<p>In adults and children older than 18 months¹, a single serological assay for initial detection of serological evidence of past or present infection is recommended prior to supplementary nucleic acid testing (NAT) for evidence of viraemic infection.</p> <p><i>Conditional recommendation, low quality of evidence</i></p>
Detection of viraemic infection	<ul style="list-style-type: none"> Directly following a reactive HCV antibody serological test result, the use of quantitative or qualitative NAT for detection of HCV RNA is recommended as the preferred strategy to diagnose viraemic infection. <p><i>Strong recommendation, moderate/low quality of evidence</i></p> An assay to detect HCV core (p22) antigen, which has comparable clinical sensitivity to NAT, is an alternative to NAT to diagnose viraemic infection⁴. <p><i>Conditional recommendation, moderate quality of evidence</i></p>
Assessment of HCV treatment response	<ul style="list-style-type: none"> Nucleic acid testing for qualitative or quantitative detection of HCV RNA should be used as test of cure at 12 or 24 weeks (i.e sustained virological response (SVR12 or SVR24)) after completion of antiviral treatment. <p><i>Conditional recommendation, moderate/low quality of evidence</i></p>

Abbreviations: DBS: dried blood spot; IVD: in vitro diagnostics; NAT: nucleic acid test; RDT: rapid diagnostic test

*The GRADE system (Grading of Recommendations, Assessment, Development and Evaluation) was used to categorise the strength of recommendations as strong or conditional (based on consideration of the quality of evidence, balance of benefits and harms, acceptability, resource use and programmatic feasibility) and the quality of evidence as high, moderate, low or very low.

¹ HCV infection can be confirmed in children under 18 months only by virological assays to detect HCV RNA, because transplacental maternal antibodies remain in the child's bloodstream up until 18 months of age, making test results from serology assays ambiguous.

² Laboratory-based immunoassays include enzyme immunoassay (EIA), chemoluminescence immunoassay (CLIA), and electrochemoluminescence assay (ECL).

³ Assays should meet minimum acceptance criteria of either WHO prequalification of IVDs or a stringent regulatory review for IVDs. All IVDs should be used in accordance with manufacturers' instructions, and where possible at testing sites enrolled in National or International External Quality Assessment Scheme.

⁴ A lower level of analytical sensitivity can be considered, if an assay is able to improve access (i.e. 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 would identify 95% of those with viraemic infection, based on available data.

INTERVENTIONS TO PROMOTE UPTAKE OF HEPATITIS TESTING AND LINKAGE TO CARE

USE OF DRIED BLOOD SPOT (DBS) SPECIMENS FOR SEROLOGY AND NUCLEIC ACID TESTING

Topic	Recommendations*
Serological testing	<ul style="list-style-type: none"> The use of DBS specimens for HBsAg and HCV antibody serology testing¹ may be considered in settings where: <ul style="list-style-type: none"> - 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 (e.g. in drug treatment programmes, prisons). <p><i>Conditional recommendation, moderate (HBV)/low (HCV) quality of evidence</i></p>
Detection of viraemia (Nucleic acid testing)	<ul style="list-style-type: none"> The use of DBS specimens to test for HBV DNA and HCV RNA for diagnosis of HBV and HCV viraemia¹, respectively, may be considered in settings where: <ul style="list-style-type: none"> - 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 (e.g. in drug treatment programmes, prisons). <p><i>Conditional recommendation, low (HBV)/moderate (HCV) quality of evidence</i></p>

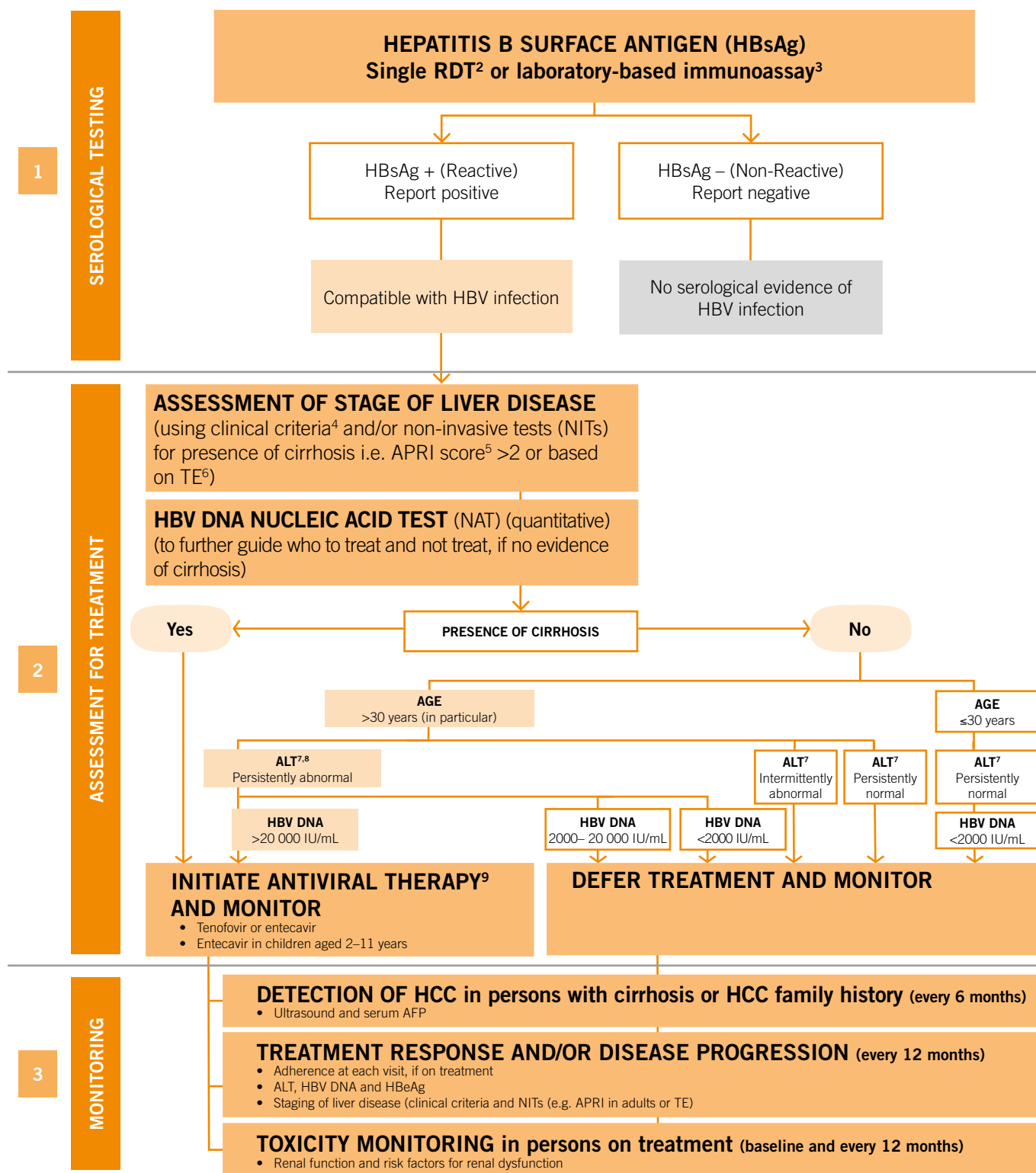
OTHER INTERVENTIONS TO IMPROVE UPTAKE OF TESTING AND LINKAGE TO CARE

Topic	Recommendations*
Uptake of testing and linkage to care	<ul style="list-style-type: none"> All facility- and community-based hepatitis testing services should adopt and implement strategies to enhance uptake of testing and linkage to care. <i>Strong recommendation, moderate quality of evidence</i> The following evidence-based interventions should be considered to promote uptake of hepatitis testing and linkage to care and treatment initiation: (<i>Conditional recommendations</i>) <ul style="list-style-type: none"> - Peer and lay health worker support in community-based settings (<i>moderate quality of evidence</i>). - Clinician reminders to prompt provider-initiated, facility-based HBV and HCV testing in settings that have electronic records or analogous reminder systems (<i>very low quality of evidence</i>). - Provision of hepatitis testing as part of integrated services within mental health/substance use services (<i>very low quality of evidence</i>).

*The GRADE system (Grading of Recommendations, Assessment, Development and Evaluation) was used to categorise the strength of recommendations as strong or conditional (based on consideration of the quality of evidence, balance of benefits and harms, acceptability, resource use and programmatic feasibility) and the quality of evidence as high, moderate, low or very low.

1. Well-functioning laboratory specimens referral network and system for return of results should be in place to maximize the impact of DBS specimens. There are currently few assays where the manufacturer's instructions state that DBS specimens are validated for use. Therefore, currently use of DBS specimens would be considered "off-label".

SUMMARY ALGORITHM FOR DIAGNOSIS, TREATMENT AND MONITORING¹ OF CHRONIC HBV INFECTION



Abbreviations: RDT: rapid diagnostic test; ALT: alanine aminotransferase; APRI: aspartate aminotransferase-to-platelet ratio index; TE: Transient elastography; HCC: Hepatocellular carcinoma; AFP: Alpha fetoprotein

1. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015.

2. In settings or populations with a low HBsAg seroprevalence <0.4%, confirmation of HBsAg positivity on the same immunoassay with a neutralization step or a second different RDT assay for detection of HBsAg may be considered.

3. Laboratory-based Immunoassays include Enzyme Immunoassay (EIA), chemoluminescence immunoassay (CLIAs), and electrochemoluminescence assay (ECL)

4. Decompensated cirrhosis is defined by the development of 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.

5. Aspartate aminotransferase (AST)-to-platelet ratio index (APRI) is a simple index for estimating hepatic fibrosis based on a formula derived from AST and platelet concentrations.

The formula for calculating the APRI score is: $APRI = (AST/AST\ ULN) \times 100 / \text{platelet count } (10^9/L)$. Most recommend using 40 IU/L as the value for AST upper limit of normal (ULN).

An online calculator can be found at: <http://www.hepatitisc.uw.edu/page/clinical-calculators/apri>

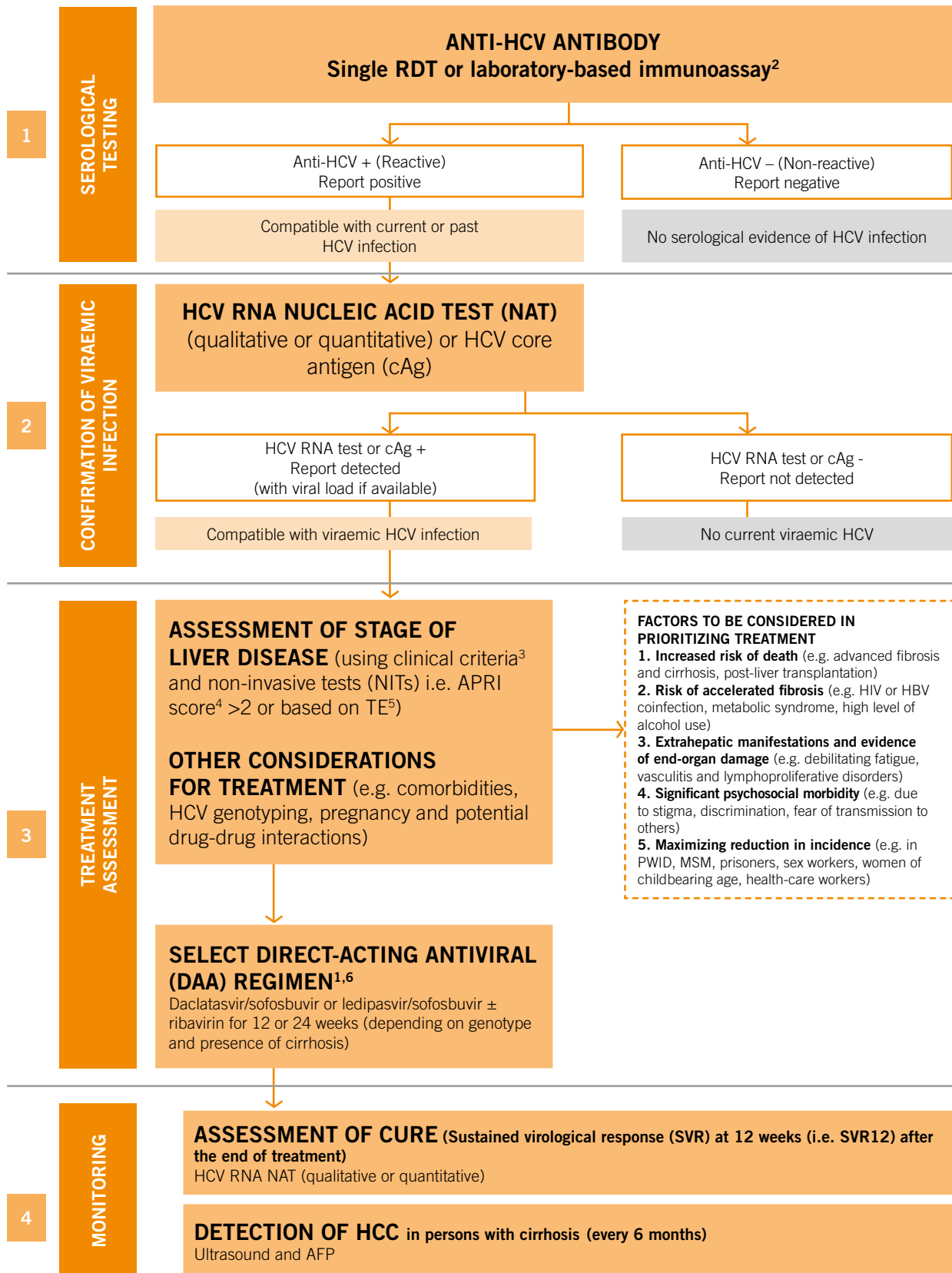
6. Transient elastography (Fibroscan): A technique to measure liver stiffness (as a surrogate for fibrosis)

7. ALT levels fluctuate in persons with chronic hepatitis B and require longitudinal monitoring to determine the trend. Upper limits for normal ALT have been defined as below 30 U/L for men and 19 U/L for women, though local laboratory normal ranges should be applied. Persistently normal/abnormal may be defined as three ALT determinations below or above the upper limit of normal, made at unspecified intervals during a 6–12-month period or predefined intervals during 12-month period

8. Where HBV DNA testing is not available, treatment may be considered based on persistently abnormal ALT levels, but other common causes of persistently raised ALT levels such as impaired glucose tolerance, dyslipidaemia and fatty liver should be excluded

9. Initiate antiviral therapy with tenofovir alone only after exclusion of HIV-coinfection

SUMMARY ALGORITHM FOR DIAGNOSIS, TREATMENT AND MONITORING¹ OF CHRONIC HCV INFECTION



Abbreviations: RDT: rapid diagnostic test; APRI: aspartate aminotransferase-to-platelet ratio index, TE: Transient elastography; PWID: People who inject drugs; MSM: Men who have sex with men; HCC: Hepatocellular carcinoma; AFP: Alpha fetoprotein

1. Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection. Updated version, April 2016. Geneva: World Health Organization 2016;

2. Laboratory-based Immunoassays include Enzyme Immunoassay (EIA), chemoluminescence immunoassay (CLIAs), and electrochemoluminescence assay (ECL)

3. Decompensated cirrhosis is defined by the development of 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.

4. Aspartate aminotransferase (AST)-to-platelet ratio index (APRI) is a simple index for estimating hepatic fibrosis based on a formula derived from AST and platelet concentrations. The formula for calculating the APRI score is: $APRI = (AST/AST\ ULN) \times 100 / \text{platelet count } (10^9/L)$. Most recommend using 40 IU/L as the value for AST upper limit of normal (ULN). An online calculator can be found at: <http://www.hepatitisc.uw.edu/page/clinical-calculators/apri>

5. Transient elastography (Fibroscan) A technique to measure liver stiffness (as a surrogate for fibrosis)

6. Caution: There is a potential but uncertain risk of HBV reactivation during or after HCV clearance. Prior to starting DAA therapy, test for HBV infection (HBsAg, HBeAg, and HBV DNA) to assess indication for HBV treatment. Continue careful monitoring after completion of DAA therapy, including for HCC.

Global Hepatitis Programme

Department of HIV/AIDS

20, avenue Appia
1211 Geneva 27
Switzerland

E-mail: hepatitis@who.int

<http://www.who.int/hepatitis>