RECOMMENDATIONS AND GUIDANCE ON

HEPATITIS C VIRUS SELF-TESTING

July 2021

Web Annex A. Process for guidelines development
Recommendations and guidance on hepatitis C virus self-testing. Web Annex A. Process for guidelines development


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This publication forms part of the WHO guideline entitled Recommendations and guidance on hepatitis C virus self-testing. It is being made publicly available for transparency purposes and information, in accordance with the WHO handbook for guideline development, 2nd edition (2014).
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Process for guidelines development

1. **Overview**
The WHO Global HIV, Hepatitis and Sexually Transmitted Infections Programmes (WHO HHS) led the development of these guidelines. These guidelines were developed in accordance with procedures established by the WHO Guidelines Review Committee and the WHO Handbook for guideline development (1). The recommendation in the guidelines is based on the GRADE approach to reviewing evidence and formulating recommendations (2).

2. **Contributors to the guidelines**
The guideline development process involved the formation of five main groups to guide and implement the process. Each group played a specific role, as described below. The members of these groups and other contributors are listed in the Acknowledgements.

1. **WHO Guideline Steering Group (GSG).** The GSG, which is responsible for overall coordination and guidance of the guidelines development process, was led by the Testing, Prevention and Population Unit within the WHO HHS. Participants included other units and WHO staff members from this department as well as from the Department of Regulation and Prequalification and the Department of Safety and Vigilance. This group also included WHO technical staff from all WHO regions.

2. **Guideline Development Group (GDG).** This group formulated the new WHO recommendation, including implementation and service delivery considerations. The group also reviewed and approved the final content of this guidelines document. It consisted of 18 members, with a balanced representation of geographic regions, gender and backgrounds, including academia and research, programme implementation and policy, and community organizations and networks. The group members were selected in coordination with the GSG and WHO country and regional offices. The GSG reviewed curricula vitae, declarations of interest and confidentiality agreements. The proposed membership list was posted for public review and comment and then finalized.

3. **External Review Group (ERG).** ERG members were responsible for peer review of these guidelines. This group was selected in consultation with the WHO GSG to assure geographic and gender balance. It comprised 32 peer reviewers from academia, policy and research, programme implementation, and community organizations, including networks of key and vulnerable populations.
4. **External guideline contributors, led by a methodologist.** With oversight by the guideline methodologist and with input from members of the WHO GSG and GDG, an independent team of experts conducted a systematic review of evidence on HCVST. Additionally, evidence on values and preferences, feasibility and cost-effectiveness was compiled and summarized by the review team.

5. **External partners and observers.** Representatives of the United States Agency for International Development (USAID), the United States Centers for Disease Control and Prevention (CDC), the Global Fund to Fight HIV, Tuberculosis and Malaria, Unitaid, the Foundation for Innovative New Diagnostics (FIND) and the Ministry of Health of Indonesia attended the GDG meeting as observers. These organizations are potential donors and implementers of the proposed guidelines and have a long history of collaboration with the WHO HHS. The Acknowledgements and Web Annex B provide the names of observers who participated in the GDG meeting.

All members of the GDG, non-WHO staff participating in meetings or guideline development, and external peer reviewers submitted declarations of interest and confidentiality statements to the WHO secretariat. The WHO secretariat and the GSG reviewed all declarations and found no conflicts of interest sufficient to preclude any GDG member from participating fully in the development of the guidelines. Web annex A provides a full compilation and a summary of these declarations of interests.

3. **Defining the scope of the guidelines**
This publication is linked to the 2017 WHO Guidelines on testing for hepatitis B and C and will be part of WHO’s forthcoming Consolidated guidelines for testing, prevention, care and treatment of persons with chronic hepatitis B and C infection. To assess the need for these guidelines, WHO convened expert consultations and scoping meetings in 2019 and 2020. Based on the outcomes of these meetings, between August 2020 and May 2021, the WHO HHS, along with the GDG, conducted a process to develop guidelines on HCVST. The ERG also provided support with peer review of documents.

4. **Development of recommendations**
To support the development of these guidelines, WHO commissioned a systematic review of available evidence on HCVST. This review also included available evidence on HIVST. In addition, WHO worked closely with FIND to conduct studies of values and preferences, usability/feasibility and cost-effectiveness, gathering further evidence and identifying potential implementation considerations.

The GDG, along with WHO, developed a population, intervention, comparator, outcome (PICO) question: “Should HCVST be offered as an additional approach for HCV testing services?” The GDG then finalized this PICO question and defined the outcomes and stratifications of interest (Table 1). In an
online survey, the GDG members ranked the importance of each outcome on the GRADE rating scale of 1–9 (0–3: not important; 4–6: important; 7–9: critical). Once the PICO question and priority outcomes were agreed, external researchers, supported by the WHO team, conducted the systematic review.

Table 1. PICO question to inform the development of the guidance on HCVST

<table>
<thead>
<tr>
<th>Question: Should HCV self-testing be offered as an additional approach for HCV testing services?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
</tr>
<tr>
<td>Intervention</td>
</tr>
<tr>
<td>Comparator</td>
</tr>
<tr>
<td>Outcomes</td>
</tr>
</tbody>
</table>

The systematic review team developed a protocol to review the relevant scientific evidence. The independent methodologist, Nandi Siegfried, assessed and reviewed the protocol, as did the GDG, GSG and WHO secretariat. The methodologist advised the review team on analytical decisions and synthesis and the grading of evidence. The review of values and preferences studies related to HCVST was included as an additional component of the systematic review. Studies providing information on the feasibility and cost-effectiveness of HCVST also were included and summarized.

The GDG worked closely with the guideline methodologist to appraise the evidence, using GRADE methodology. This appraisal included assessment of the risk of bias for all studies included in the systematic review, using the Cochrane Collaboration’s risk of bias tool for randomized controlled trials (RCT) (3) and the ROBINS-I tool for non-randomized studies (4).

WHO subsequently convened two virtual technical consultations (December 2020 and March 2021) with the GDG. Based on the evidence reviewed and presented at this consultation, the GDG made a new recommendation on HCVST. The methodologist facilitated the GDG discussion and formulation of the recommendation. External peer review was then completed in May 2021.

5. GRADE systematic review

Table 1 presents the PICO question that informed development of the guidance on HCVST. The systematic review team conducted a comprehensive, systematic search of the published literature, conference abstracts and grey literature for studies assessing the effectiveness of HCVST from January 1, 2010 through December 16, 2020. The protocol was prospectively registered with PROSPERO (CRD42021235825). Web annex C provides details on the systematic review methodology.
According to GRADE methodology, indirect evidence can be considered where direct evidence is not available (5). A decision was made a priori in consultation with the GSG and the GDG to include evidence on HIVST to inform the HCVST review, given the relevance of HIVST and available living systematic review procedures that were established for the 2019 WHO guidelines on HIV testing services. In order to maximize the applicability of evidence on HIVST to HCVST, comparable outcomes included in both reviews were identified (Table 2), and the HIVST review was updated through June 2020. This review follows GRADE methods which have been detailed in the 2019 WHO guidelines on HIV testing services (6) and elsewhere (7, 8).

Table 2. Outcomes comparable across HCVST and HIVST systematic reviews

<table>
<thead>
<tr>
<th>HCVST review outcomes</th>
<th>Corresponding HIVST review outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uptake of testing services</strong> (GDG ranking 7.8 – critical)</td>
<td>Uptake of testing services</td>
</tr>
<tr>
<td>proportion of participants who completed HCV testing among those randomized in a specified time frame</td>
<td></td>
</tr>
<tr>
<td><strong>HCV positivity</strong> (GDG ranking 6.4 – important)</td>
<td>HIV positivity</td>
</tr>
<tr>
<td>proportion of people diagnosed with HCV or proportion of people who had a reactive HCV antibody test (self-test, rapid test or enzyme immunoassay (EIA)) among those randomized (adjusted to exclude people aware of their HCV chronic infection status before testing and/or on treatment)</td>
<td></td>
</tr>
<tr>
<td><strong>Linkage to additional testing</strong> (GDG ranking 8.0 – critical)</td>
<td>Linkage to additional testing</td>
</tr>
<tr>
<td>testing by a trained provider after reactive HCVST results, including a) additional antibody testing and/or b) viral load (PCR) and/or HCV core Ag testing to confirm chronic infection</td>
<td></td>
</tr>
<tr>
<td><strong>Linkage to clinical assessment and/or treatment initiation</strong> among those randomized (GDG ranking 8.0 – critical)</td>
<td>Linkage to clinical assessment and/or treatment initiation</td>
</tr>
<tr>
<td><strong>Number/proportion cured or initiated and completed treatment</strong> among those randomized or diagnosed with chronic HCV infection (GDG ranking 7.4 – critical)</td>
<td>Not applicable to HIV</td>
</tr>
<tr>
<td><strong>Misuse related to self-tests</strong>, for example coercion or forced testing (GDG ranking 5.8 – important)</td>
<td>Misuse related to self-tests</td>
</tr>
<tr>
<td><strong>Social harm (including adverse events, violence, device failures) related to testing</strong> (GDG ranking 6.4 – important)</td>
<td>Social harm (including adverse events, violence, device failures) related to testing</td>
</tr>
</tbody>
</table>

Data stratified by population type (general population and key populations) were analysed by the systematic review team and presented to the GDG, as both population types can be at heightened risk for HCV in different settings, particularly people who inject drugs, men who have sex with men and the general population in certain high prevalence settings. Additionally, although the HIVST review focused on randomized studies, observational studies were searched to identify any HIVST studies that were specifically conducted among people who inject drugs, as this was identified as a priority population for HCVST.
6. Additional evidence

6.1 Values and preferences and feasibility
Information on values and preferences was collected and analysed as part of the HCVST systematic review. Studies included were qualitative and quantitative observational studies that related to the acceptability and feasibility of HCVST among self-testers and health workers or health-care providers. Studies that reported on community-based rapid testing and self-sampling for HCV testing were also included. Additionally, the systematic review team included values and preferences literature identified as part of the WHO’s 2019 HIVST review. All data were then summarized.

WHO coordinated with FIND to conduct additional multi-country studies of feasibility and of values and preferences to supplement this review of the evidence. Web annexes D and E present the full reports.

6.2 Resource use
The systematic review team summarized available evidence on cost and cost-effectiveness specific to HCVST as part of the systematic review. A summary of cost and cost-effectiveness from the HIVST review was also included for reference.

WHO also coordinated with FIND and the University of Bristol to complete a multi-country HCVST cost-effectiveness modelling study. This evidence was used to supplement existing literature. Web Annex F provides full details.

7. Evidence assessment
Following the WHO guideline development process, the GDG formulated the recommendation according to the GRADE DECIDE approach. The GDG decision was guided by consideration of the potential benefits and harms related to HCVST. In addition, stakeholder values and preferences, acceptability, feasibility, resource use and considerations of human rights and equity contributed to determining the strength of the recommendation (Table 3) (9).

Table 3. Domains considered when assessing the strength of recommendations

<table>
<thead>
<tr>
<th>Domain</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefits and harm</td>
<td>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.</td>
</tr>
<tr>
<td>Certainty of evidence</td>
<td>High certainty of evidence is likely to lead to a strong recommendation.</td>
</tr>
<tr>
<td>Values and preferences (of providers and stakeholders)</td>
<td>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.</td>
</tr>
<tr>
<td>Cost/financial implications</td>
<td>Lower costs (monetary, infrastructure, equipment or human resources) or greater cost-effectiveness contribute to a strong recommendation.</td>
</tr>
</tbody>
</table>
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.

The GRADE approach specifies four levels of certainty of evidence (Table 4). Based on the certainty of evidence, the strength of a recommendation can be either strong or conditional.

Table 4. Interpretation of the four GRADE levels of evidence

<table>
<thead>
<tr>
<th>Certainty of evidence</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>We are very confident that the true effect lies close to the estimate of effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are moderately confident in the estimate of effect. The true effect is likely to be close to the estimate of effect, but it could be substantially different.</td>
</tr>
<tr>
<td>Low</td>
<td>Our confidence in the estimate of effect is limited. The true effect may be substantially different from the estimate of effect.</td>
</tr>
<tr>
<td>Very low</td>
<td>We have very little confidence in the estimate of effect. Any estimate of effect is very uncertain.</td>
</tr>
</tbody>
</table>

8. Developing the recommendation

As noted, WHO convened two virtual technical consultations with the GDG (December 2020 and March 2021). During this same period, the GSG met three times. The GDG meeting in December 2020 included review of background materials, presentation of the systematic review protocol and preliminary findings from the values and preferences, feasibility and cost-effectiveness analyses. The GDG meeting in March 2021 included presentation of the final systematic review findings and supportive evidence.

At the beginning of the March 2021 meeting, WHO and the GDG determined that the goal for decision-making would be to reach consensus, defined as agreement of the group, but that, if consensus could not be reached, a vote of at least 60% would be required to approve the recommendation. In discussion facilitated by the methodologist during the March meeting, GDG members considered the systematic review evidence and supplementary evidence on values and preferences, feasibility and cost-effectiveness.

During the meeting the GDG discussed both the evidence on HCVST and additional evidence on HIVST. The group determined that evidence from HIVST was highly applicable to HCVST, with similar outcomes and effects anticipated and overlapping populations in many settings. Following this discussion, the GDG reached consensus on the direction, strength and wording of the recommendation. Additional remarks were added to the recommendation to address key implementation considerations.

WHO then drafted the full guidelines and circulated them electronically to the GDG, GSG and ERG for comments and feedback. All responses were considered and addressed as appropriate in the final draft. The final guidelines will be published electronically on the WHO website with Web annexes.
9. References