### 4.9. Monitoring treatment response HCV

#### Decision-making tables – PICO 9

**Monitoring for treatment response using HCV Ag testing in individuals with confirmed active HCV infection**: Among individuals receiving antiviral treatment for HCV, what is the diagnostic accuracy of HCV core antigen versus NAT for HCV RNA qualitative detection (and/or) quantification to confirm successful treatment response with viral clearance?

<table>
<thead>
<tr>
<th>Population:</th>
<th>Patients receiving treatment for HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention:</strong></td>
<td>HCV core antigen assay</td>
</tr>
<tr>
<td><strong>Comparison:</strong></td>
<td>NAT for HCV RNA detection (and/or) quantification</td>
</tr>
<tr>
<td><strong>Outcomes:</strong></td>
<td>Diagnostic accuracy (Sensitivity and specificity, TN, TP, FN, and FP)</td>
</tr>
</tbody>
</table>

1. **Background:**
   - HCV core antigen (HCV cAg) testing was developed as an alternative to NAT for diagnosis of active HCV infection. HCV nucleocapsid peptides 22 (p22) are released into plasma during viral assembly and can be detected throughout the course of HCV infection.
   - Detection of HCV viraemia is also important during treatment of chronic HCV infection.
   - Current guidelines recommend verification of virological activity pre-treatment with the measurement of a baseline HCV RNA quantitative measurement (viral load) by NAT. For interferon-based treatments, HCV RNA viral load is assessed at week 4 of therapy for the “rapid viral response” (RVR) to help predict efficacy of therapy, and repeated at week 6 if elevated at week 4 to see further viral response and guide whether treatment should be continued.
   - NAT for HCV RNA is performed again at week 12 (early viral response, EVR), at the end of treatment, and 12 and 24 weeks after therapy is completed to test for cure, “sustained viral response” (SVR).
   - New, direct-acting antivirals (DAA) have made treatment for HCV much easier with oral rather than parenteral administration and shorter, more effective regimens that are likely to be easier to adhere to making access to affordable diagnostic and monitoring assays even more important. However, it is important to note that, ultimately, treatment monitoring may not be required with the routine use of DAAs.
   - This PICO addresses the question of whether HCV cAg can be used as a tool for assessing response to treatment for HCV infection.
2. Draft recommendation(s):

3. Summary and quality of evidence

A systematic review (see SR_PICO 9) was commissioned to address the above PICO question. This aimed to examine the utility of HCV cAg monitoring for those on HCV treatment (PICO 9).

Summary of results

Sensitivity and specificity of Abbott ARCHITECT HCV cAg assay compared to HCV RNA assessed at baseline, at week 4 of interferon-based therapy (early viral response), and at week 24 after completion of treatment (sustained viral response)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>N</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feng, 2014</td>
<td>32</td>
<td>100%</td>
<td>N/A</td>
<td>100%</td>
<td>88.9% (68.4%, 100%)</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Loggi, 2013</td>
<td>35</td>
<td>100%</td>
<td>N/A</td>
<td>73.5% (58.7%, 88.4%)</td>
<td>100%</td>
<td>100%</td>
<td>94.1% (82.9%, 100%)</td>
</tr>
<tr>
<td>Moscato, 2010</td>
<td>23</td>
<td>N/A</td>
<td>N/A</td>
<td>100%</td>
<td>70% (41.6%, 98.4%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N: number of subjects; HCV: hepatitis C virus, Ag: antigen, Se: sensitivity, Sp: specificity, CI: confidence interval, N/A: not applicable as cannot be calculated from study data

Sensitivity and specificity of HCV core antigen in prediction of sustained viral response (SVR) after initiation of interferon-based treatment

□ High
□ Moderate
□ Low
□ Very low
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>N (N to achieve SVR)</th>
<th>Index test</th>
<th>Timing of test after treatment start</th>
<th>Change in HCVcAg</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feng, 2014</td>
<td>32 (21)</td>
<td>Abbott ARCHITECT</td>
<td>6 days</td>
<td>Log 10</td>
<td>95.2%</td>
<td>70%</td>
</tr>
<tr>
<td>Loggi, 2013</td>
<td>90 (57)</td>
<td>Fujirebio Lumipulse</td>
<td>7 days</td>
<td>Absolute</td>
<td>79.4%</td>
<td>88.5%</td>
</tr>
<tr>
<td>Moscato, 2010</td>
<td>44 (10)</td>
<td>Fujirebio Lumipulse</td>
<td>7 days</td>
<td>Absolute</td>
<td>57.1%</td>
<td>93.3%</td>
</tr>
</tbody>
</table>

HCV: hepatitis C virus; N: number

**Conclusions:**

- HCV core Ag assays can have high sensitivity (up to 93.4% for certain commercialized assays), high specificity, and good correlation with HCV RNA to a detection limit of roughly 3000 IU/mL.
- The data on HCV core Ag for treatment monitoring and as a test of cure is too limited to reach reliable conclusions.

**Quality of evidence**

*Refer GRADE table in footnote*

**4. Risks/benefits**

**Benefits**

- HCV cAg testing by immunoassay format has the potential to be less costly and less complicated to perform than HCV RNA by NAT. However, these immunoassays still require sophisticated laboratory equipment and therefore skilled staff to operate. Access to cold storage and constant electricity is required for the current types of assays available for HCV cAg testing.
- Results for patients on antiviral treatment being monitored for sustained viral response may be available more rapidly as a result of decentralized testing.
Risks

- Due to reduced analytical sensitivity and limited understanding of kinetics of HCV cAg compared to HCV RNA by NAT, individuals on antiviral treatment may be misclassified as responding to treatment, but may have persisting viraemia below the limits of detection of the assay.

5. Acceptability, values and preferences

A values and preferences survey of implementers and users of hepatitis B and C testing services was carried out by FIND in September 2015. A total of 104 respondents from 43 (20 high-income, 23 low- and middle-income) countries participated. Relating to this PICO,

- As assay (platform) for detection of HCV cAg is available in India, Indonesia, Former Yugoslav Republic of Macedonia, Viet Nam, Turkey. The platform is available in South Africa but not currently being used for HCV cAg detection.
- Currently only 11% of respondents are using HCV cAg as a test of cure.
- 44% of respondents preferred a 12-week follow up for testing after completion of therapy, while 19% and 15% preferred a 4- or 8-week follow up.
- 47% of patients preferred to have the same test for monitoring and detection, ideally in decentralized settings.
- Free text comments from respondents included concerns regarding the sensitivity and specificity of cAg, but that it was potentially easier to do. One comment stated that it could be acceptable if it increased access to treatment.
- A larger number of respondents felt that the cost of testing for HCV RNA by NAT was considered more of a barrier than that of HCV cAg.
- As stated previously, 47% of respondents in low- and middle-income countries would prefer testing at POC, even at the cost of sensitivity.

Patients:

- Patients at risk of progressive liver disease will benefit from reduced disease progression and related mortality and morbidity, if treatment is provided as a result of wider access to testing programmes.

Community:

- To identify the individuals who require assessment and treatment would be an effective use of resources.
- As testing and treatment programmes are scaled up, the numbers developing
progressive disease and serious outcomes (HCC and complications of advanced liver disease), premature morbidity and mortality within the community will be reduced, and so also the burden of disease to societies where the disease is most prevalent.

**Health-care workers:**

- Appropriate use of resources to channel treatment to patients with higher risk of complication in the medium- and short term
- Will require training in the use of testing equipment if being used in the near-POC setting
- Appropriate reporting and recording of results.

**Laboratory:**

- Will require purchasing of the appropriate platform and reagents for the HBsAg detection assay
  Will require training for HCV cAg test: careful sample processing is necessary for HCV cAg assay to lyse viral particles, expose antigen and dissociate antibody from antigen and optimize the detection for HCVcAg.

6. **Equity, ethics and human right implications**

   Will the recommendation raise questions around equity?

   - Equity will improve as a result of decentralization of testing, however, still improvement of access to the testing facilities is necessary.
   - Regional and country variability in access to treatment.

   Are there ethical implications to this recommendation?

   - Ethical consideration for the possibility that WHO could recommend a suboptimal testing strategy.

7. **Resource use and financial implications**

   **Materials/equipment:**

   - Cost of testing platform and reagents
   - Other laboratory consumables

   Are the resources required small?

   □ No
   □ Probably
   □ Uncertain
Training and supervision:
- Appropriate training of laboratory staff
- Quality control programmes
- If using near-POC assays, appropriate training of testing providers.

Other:
- Cost of transportation of specimens to the laboratory

Possible procurement costs:

<table>
<thead>
<tr>
<th>Assay format</th>
<th>Indicative cost (US$) per test</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDTs</td>
<td>0.50–2.00 (10 for oral fluid RDTs)</td>
<td>MSF, WHO</td>
</tr>
<tr>
<td>EIA</td>
<td>0.50–1.70</td>
<td>WHO</td>
</tr>
<tr>
<td>HCV Ag</td>
<td>25–50</td>
<td>MSF</td>
</tr>
<tr>
<td>Quantitative NAT for HCV RNA</td>
<td>10–45</td>
<td>MSF, UNITAID</td>
</tr>
<tr>
<td>Qualitative NAT for HCV RNA</td>
<td>43–51</td>
<td>UNITAID</td>
</tr>
</tbody>
</table>

- Feasibility and constraints to implementation

Are any major barriers expected for the implementation of this recommendation?
- Regional and country variability in access to treatment and procurement of testing equipment and services
- With regard to HCV cAg, availability of a local laboratory, which is able to procure the testing platform and reagents required for testing.

Is the option feasible to implement?
- No
- Probably
- Uncertain
- Yes
- Varies
### 8. Relevance to different settings/populations

*Will this recommendation be most relevant for particular settings (e.g. endemicity)?*

- HCV cAg testing will be more relevant to populations that presently rely on centralized laboratory testing for HCV RNA for confirmation of status.
- The recommendations are less likely to be relevant in high-income settings where there is already access to established hepatitis C testing and treatment programmes.

### 9. Rationale for recommendation:


### 10. Strength of recommendation


### 11. Implementation considerations

- Optimize test for asymptomatic patients in primary-care settings or in the community where the HCV endemic is high.

### 12. Research gaps

- The kinetics of HCV cAg with treatment needs to be evaluated further, particularly in the context of new DAA regimens.
- More rigorous assessment of covariates is required in studies assessing HCV cAg or NATs for treatment monitoring or as a test of cure, such as HIV or HBV coinfection or genotype.
- Is treatment monitoring and/or confirmation of cure necessary with DAA regimens? If so, what would be the optimal timing of testing?
- When is the best time-point to test for cure with HCV core Ag?
- Development of multiplex instrument with other disease diagnosis such as HIV, HBV, and TB at health centre.
- HCVcAg assay to detect the variants of HCV.
### GRADE Summary of findings

#### SR outcome 1: Diagnostic accuracy at SVR

<table>
<thead>
<tr>
<th>Index test</th>
<th>Outcome measure</th>
<th># Studies (# samples)</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
<th>Effect*</th>
<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott ARCHITECT HCV Ag Assay</td>
<td>Sensitivity</td>
<td>2 (67)</td>
<td>RCT, cohort</td>
<td>Low&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Low&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Moderate&lt;sup&gt;e&lt;/sup&gt; (−1)</td>
<td>Low&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Low&lt;sup&gt;1.21&lt;/sup&gt;</td>
<td>100%*</td>
<td>Moderate&lt;sup&gt;○○○&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>2 (67)</td>
<td>RCT, cohort</td>
<td>Low&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Moderate&lt;sup&gt;2&lt;/sup&gt; (−1)</td>
<td>Moderate&lt;sup&gt;e&lt;/sup&gt; (−1)</td>
<td>Low&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Low&lt;sup&gt;1.23&lt;/sup&gt;</td>
<td>94–100%*</td>
<td>Low&lt;sup&gt;○○○&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

#### SR outcome 2: Predictive accuracy of SVR

<table>
<thead>
<tr>
<th>Index test</th>
<th>Outcome measure</th>
<th># Studies (# individuals)</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
<th>Effect*</th>
<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott ARCHITECT HCV Ag Assay</td>
<td>Sensitivity</td>
<td>1 (23)</td>
<td>Cohort</td>
<td>Low&lt;sup&gt;1&lt;/sup&gt;</td>
<td>NA&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Moderate&lt;sup&gt;e&lt;/sup&gt; (−1)</td>
<td>NA&lt;sup&gt;4&lt;/sup&gt;</td>
<td>95.2%**</td>
<td>Low</td>
<td>Low&lt;sup&gt;○○○&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>1 (23)</td>
<td>Cohort</td>
<td>Low&lt;sup&gt;3&lt;/sup&gt;</td>
<td>NA&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Moderate&lt;sup&gt;e&lt;/sup&gt; (−1)</td>
<td>NA&lt;sup&gt;4&lt;/sup&gt;</td>
<td>70%**</td>
<td>Low</td>
<td>Low&lt;sup&gt;○○○&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fujirebio Lumipulse Ortho HCV Ag</td>
<td>Sensitivity</td>
<td>2 (134)</td>
<td>Cohort</td>
<td>Moderate&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Moderate&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Moderate&lt;sup&gt;e&lt;/sup&gt; (−1)</td>
<td>Moderate&lt;sup&gt;4&lt;/sup&gt;</td>
<td>57.1–79.4%*</td>
<td>Very low</td>
<td>Low&lt;sup&gt;○○○○&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td>2 (134)</td>
<td>Cohort</td>
<td>Moderate&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Moderate&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Moderate&lt;sup&gt;e&lt;/sup&gt; (−1)</td>
<td>Moderate&lt;sup&gt;4&lt;/sup&gt;</td>
<td>88.5–99.3%*</td>
<td>Very low</td>
<td>Low&lt;sup&gt;○○○○&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

* Results reported are a range across studies or **individual result, NA: not applicable
References

