WHO/HIV/2014.35

Global Hepatitis Programme

Guideline development for Hepatitis C virus Screening, Care and Treatment in low- and middle-income countries
PICO 2 Testing (RNA Testing) – Decision Making Table

Health system and public health evidence to recommendations framework

When should HCV RNA tests be performed: At receipt of positive HCV antibody test result or in the context of assessment for HCV therapy?

Population: People who are HCV antibody positive

Intervention: HCV RNA testing at the time of receipt of a positive HCV antibody result

Comparison: HCV RNA test in the context of HCV care as part of assessment for HCV therapy

Outcomes: Number of cases of HCV transmission, number achieving sustained virological response (SVR), number of cases of decompensated liver diseases/hepatocellular carcinoma/ liver-related deaths/ all cause mortality, quality of life

Background:

The World Health Organization estimates that between 130 and 150 million people are chronically with hepatitis C virus (HCV) worldwide[1]. People with untreated HCV are at increased risk of liver cirrhosis, hepatocellular carcinoma, and liver-related mortality[2]. HCV RNA testing, which generally follows a positive anti-HCV antibody test in a clinical setting, allows the detection of current HCV infection, thus identifying individuals that require treatment and follow-up[3,4,5].

It is considered standard of care to carry out RNA testing prior to starting HCV treatment. The aim of the systematic review was to determine the optimal time at which to perform HCV RNA tests in order to establish the presence of current infection, and to reduce morbidity and mortality associated with HCV infection.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	Hepatitis C virus (HCV) infection affects more than 3% of the global population and poses a high economic burden. More than 170 million individuals are chronically infected, and it is a major cause of hepatocellular carcinoma and liver cirrhosis, resulting in 350,000 deaths each year. The diagnosis of chronic infection requires HCV RNA testing as 15-50% of those initially infected with HCV (and who have a positive antibody test) will subsequently spontaneously clear the infection. The timing at which to carry out testing was considered as part of a systematic review.	
	Are a large number of people affected?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
BENEFITS & HARMS OF THE OPTIONS	**Are the desirable anticipated effects large?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐	Eight articles were obtained for full-text appraisal[6,7,8,9,10,11,12,13]. No studies matched the complete inclusion criteria as all lacked a comparison arm and were primarily designed to address other research questions. Since the aims were different, these studies did not directly report on the outcomes of interest specified in the PICO. Therefore no studies were included for qualitative or quantitative assessment and in the absence of any directly relevant studies, neither narrative synthesis nor meta-analysis could be performed (Tables 1-3). Given that no studies were found to be directly relevant, a broadened search was carried out of systematic reviews, comment papers, and other study types in order to capture relevant studies. This included widening the search topic to include comparisons of RNA testing at any time versus no RNA testing, as opposed to testing "early" (at receipt of anti-HCV-Ab test) versus "late" (in the context of care as part of assessment for HCV treatment). This also yielded no further citations of primary studies or systematic reviews. Despite not meeting the complete PICO inclusion criteria, those articles appraised at full-text review stage are summarised in evidence Tables 1-3 for indirect evidence related to the question. There was some indirect evidence suggesting that HCV RNA testing is underutilized in populations in which it is indicated (Rein et al., 2012, Rongey et al., 2009, Sheth et al., 2012, Yoshino and Kasai, 1996). Rongey *et al.* (2009) found that predictors of receipt of an RNA test among a cohort of anti-HCV-positive US veterans included patients with abnormal transaminases, the presence of non-HCV hepatitis, and decompensated liver disease, while those aged over 65 years, and illicit drug users were significantly less likely to be HCV RNA tested. PICO 2 RNA screening systematic review	Indirect data also comes from PICO 1 and alcohol intervention.
	Are the undesirable anticipated effects small?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐		
	What is the overall certainty of this evidence?	*No included studies* ☐ *Very low* ☐ *Low* ☒ *Moderate* ☐ *High* ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
VALUES	**How certain is the relative importance of the desirable and undesirable outcomes?**	*Important uncertainty or variability* ☐ *Possibly important uncertainty or variability* ☐ *Probably no important uncertainty or variability* ☐ *No important uncertainty or variability* ☒ *No known undesirable outcomes* ☐	In the absence of high quality evidence, the relative importance of each of the desirable outcomes relative to the undesirable outcomes was considered following expert opinion within the Guidelines Committee to show no important uncertainty or variability. ***The relative importance or values of the main outcomes of interest:*** **Outcome** / **Relative importance** / **Certainty of the evidence** Number of cases of HCV transmission — No evidence SVR — No evidence Decompensated liver cirrhosis (DCC) — No evidence Hepatocellular carcinoma (HCC) — No evidence All-cause mortality — No evidence Quality of life — No evidence	
	Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐	In the absence of high quality evidence, the desirable effects were considered most likely to outweigh the undesirable by the Guidelines Committee.	

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
RESOURCE USE	**Are the resources required small?**	*No* ☒ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐	The resources required for RNA testing were considered to be substantial. Although testing at the time of diagnosis was considered to be most appropriate, an increase in cost in retesting prior to treatment was acknowledged by the committee. Without RNA testing, the true burden of disease is not understood at an individual or population level. The cost of testing was considered to be variable in different settings – in China, testing is carried out in Germany and costs $200 (USD) per patient – therefore this is carried out only prior to treatment. In Egypt, testing is cheaper ($30) and is carried out immediately following antibody testing. Advanced in testing methodology such as flexible PCR machines for BBV testing would improve the costs. ***Main resource requirements*** **Resource** — **Settings** *Training* — Blood letting; Interpretation of RNA test; Facility for testing *Supervision and monitoring* — Counselling by medical practitioner about result *Supplies* — RNA testing resources	
	Is the incremental cost small relative to the net benefits?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐	Although the increase in cost associated with earlier testing was considered to be likely, the committee considered that the incremental cost was smaller than the net benefit. Patients uninfected with HCV following spontaneous clearance would be reassured and those requiring treatment would be made aware of this.	

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
EQUITY	**What would be the impact on health inequities?**	*Increased* ☐ *Probably increased* ☐ *Uncertain* ☐ *Probably reduced* ☒ *Reduced* ☐ ***Varies*** ☐	The guidelines committee considered that early diagnosis would be likely to benefit groups of individuals of lower socio-economic status (based on expert opinion) and therefore potentially reduce health inequities.	
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐	The guidelines committee agreed that most key stakeholders would agree that early RNA testing was appropriate.	
FEASIBILITY	**Is the option feasible to implement?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐	Early RNA testing was considered to be likely to be feasible in settings where pre-treatment RNA testing was feasible.	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☒	☐

Type of recommendation	We recommend against the option	We suggest considering the option	We recommend the option
	☐	☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts	☒

Recommendation

It is suggested that RNA testing be performed directly following a positive HCV antibody test to establish the diagnosis of HCV infection rather than just as part of evaluation for therapy.
Conditional recommendation, low quality of evidence.

Justification

The available evidence showed that the benefits of early RNA testing (patient information regarding resolved or chronic infection requiring treatment and an increase in follow-up) is likely to outweigh potential harms. The recommendation is conditional given the very low quality evidence and the fact that the intervention may be more resource intensive.

Implementation considerations

Earlier testing may result in more tests carried out per patient (requiring a further test prior to treatment).
Testing should be voluntary and not mandatory.

Monitoring and evaluation

Monitoring of laboratory and clinical facilities to ensure high standards of practice are required.

Research priorities

Further research into the optimal timing of RNA testing is warranted to compare early testing with delayed testing on patient outcomes, including HCV transmission, morbidity, mortality and quality of life. Prospective cohort studies of individuals after diagnosis of HCV may provide this evidence as randomised trials of early versus later RNA testing are highly unlikely to gain ethical approval in settings where RNA testing is readily available.

Problem: [Problem]

Option: [Option]

Comparison: [Comparison]

Setting: [Setting]

Evidence profile [title]

Authors: David Hunt, Esther Aspinall, and Hamish Innes
Date: 2013-05-16
Question: When should HCV RNA tests be performed: At receipt of positive HCV antibody test result or in the context of assessment for HCV therapy?
Settings: Individuals with chronic HCV infection
Bibliography:

Table 1: Characteristics of studies among anti-HCV positive individuals receiving RNA testing, without direct comparison group, for potential indirect evidence

Study	Population	Intervention	Outcomes	Comments
Allison *et al. (*2012) **Setting:** Blood donation service, US **Study type:** Retrospective cohort	Anti-HCV positive blood donors	HCV RNA in all patients No comparison	HCV related-cirrhosis; risk factors for HCV acquisition	Aimed to describe risk factors for HCV acquisition and predictors of liver disease (cirrhosis) in a US blood donation service. All individuals tested for RNA in the study regardless of timing of infection. Found after mean 25 years of HCV infection, histologic outcomes were mild and 20% had spontaneously cleared.
Ohkoshi *et al.* (1995) **Setting:** One township, Japan **Study type:** Retrospective cohort	Anti-HCV positive undergoing annual liver function testing	HCV RNA test in all patients No comparison arm	HCV natural history, patient characteristics	Aimed to better define HCV natural history in one town in Japan. Among 63 subjects, 50 (79.4%) HCV RNA detected in serum and 40 (80%) of the 50 subjects with HCV RNA had abnormal LFTs. Six of 50 (12%) had ultrasonographic findings suggestive of cirrhosis. Concludes the viraemic patients had low rates of progressive liver disease.
Piasecki et al. (2004) **Setting:** Medical centre, US **Study type:** prospective cohort	Anti-HCV-positive (RNA+ and RNA – patients)	HCV RNA testing for spontaneous clearance	HCV RNA spontaneous clearance	Aimed to define the role of alcohol, race, and HCV or HIV co-infection on natural HCV clearance. Likelihood of spontaneous clearance of HCV may be influenced by alcohol and viral co-infections. For indirect evidence, study provides information on prevalence of RNA testing immediately after anti-HCV-ab testing.
Rein et al. (2012) **Setting:** Four large primary care service providers, US **Study type:** Retrospective cohort	Outpatients tested for anti-HCV	HCV RNA testing after receipt of anti-HCV positive test No comparison arm	RNA testing pattern/predictors	Investigating effectiveness of one-time HCV screening for people born 1945-65. Data collected from medical records for anti-HCV antibody testing and HCV RNA testing. Evidence of low HCV RNA testing rates among anti-HCV-positive. Evidence suggesting that RNA testing is not being performed in the population in which it is indicated.

Rongey et al. (2009) **Setting:** Veteran facilities, US **Study type:** Retrospective cohort	Anti-HCV-positive US veterans	HCV RNA testing (with and without routine HCV RNA testing in anti-HCV-positive individuals) No comparison arm	RNA test being performed	Aimed to determine factors influencing HCV RNA testing in US anti-HCV-positive veterans. Perceived eligibility for treatment may influence the decision to order an RNA test. Patients with abnormal transaminases, presence of non-HCV hepatitis or decompensated liver disease all significantly more likely to receive HCV RNA testing, while patients aged over 65 years and illicit drug users were significantly less likely. Results of the study include predictors of RNA testing and suggest significant underutilization of RNA testing, where treatment eligibility is used as a prompt for performing HCV RNA testing.
Scott *et al.* (2006) **Setting:** Outpatients, Alaska, US **Study type:** prospective cohort	Anti-HCV positive	HCV RNA testing soon after anti-HCV diagnosis No comparison arm	Frequency of RNA spontaneous clearance	Aims to determine frequency of spontaneous HCV RNA clearance during chronic HCV infection. Found annualized clearance rate of 0.74% per person-year (95% CI, 0.30%-1.53%). Concluded clearance is a surprisingly frequent event and is associated with low HCV RNA titres at baseline.
Sheth et al. (2012) **Setting:** Patients identified with CHC in various clinical and non-clinical settings, US **Study type:** retrospective study	Patients with CHC	Anti-HCV or RNA testing No comparison arm	Characteristics of incident HCV cases	Description of characteristics of an incident cohort of patients with CHC. Investigated anti-HCV antibody and HCV RNA testing within 60 days prior to index date, and also quantitative RNA testing after treatment initiation. Indirect evidence suggesting that RNA testing is not being performed in the population in which it is indicated, resulting in potential misdiagnosis.
Yoshino and Kasai (1996) **Setting:** Medical clinic, Japan **Study type:** Retrospective cohort	Anti-HCV-positive patients receiving annual liver function examinations	HCV RNA testing in context of long-term care No comparison arm	HCV transmission routes	Aimed to investigate initial HCV transmission routes among anti-HCV positive/ HCV-RNA negative cases compared to HCV-RNA positive cases. Indirect evidence suggesting that RNA testing is not being performed in the population in which it is indicated.

Table 2: GRADE Evidence summary – HCV RNA testing performed immediately after anti-HCV diagnosis compared with RNA testing in context of HCV care/treatment among anti-HCV positive individuals

Outcomes	**No of participants (Studies)** Follow up	**Quality of the Evidence (GRADE)**	**Relative Effect (95% CI)**	**Anticipated absolute effects**
HCV transmission	No data			
Sustained Virological Response	No data			
Adverse events	No data			
Liver-related morbidity	No data			
Mortality	No data			
Quality of Life	No data			

Table 3: Summary of other quantitative evidence of risk of receiving HCV RNA test

Outcomes	**No of participants (Studies)** Follow up	**Quality of the Evidence (GRADE)**	**Relative Effect (95% CI)**	**Reference**
What is the association between age >65 and receiving a test for HCV RNA? Outcome: receipt of RNA test	13,257 (1 study) 5 years	Very low[1]	0.79 (0.69-0.92)	(Rongey et al., 2009)
What is the association of illicit drug use on RNA testing? Outcome: receipt of RNA test	13,257 (1 study) 5 years	Very low[1]	0.94 (0.91-0.97)	(Rongey et al., 2009)
What is the association of abnormal transaminases on RNA testing? Outcome: receipt of RNA test	13,257 (1 study) 5 years	Very low[1]	1.1 (1.03-1.20)	(Rongey et al., 2009)
What is the association of non-HCV hepatitis on RNA testing? Outcome: receipt of RNA test	13,257 (1 study) 5 years	Very low[1]	1.07 (1.02-1.14)	(Rongey et al., 2009)
What is the association of decompensated liver disease (cirrhosis) on RNA testing? Outcome: receipt of RNA test	13,257 (1 study) 5 years	Very low[1]	1.2 (1.1-1.3)	(Rongey et al., 2009)

[1]Evidence ranked very low due to single observational study data; N-O quality appraisal of study, 5 out of maximum 9 points.

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References

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[1] World Health Organization, 2012

[2] Villano *et al.* 1997

[3] Rongey *et al.* 2009

[4] Scott *et al.* 2006

[5] Piasecki *et al.* 2004

[6] Scott *et al.* 2006

[7], Sheth *et al.* 2012

[8] Rein *et al.* 2012

[9] Allison *et al.* 2012

[10] Piasecki *et al.* 2004

[11] Ohkoshi *et al.* 1995

[12] Yoshino and Kasai 1996

[13] Rongey et al., 2009

Definitions for ratings of the certainty of the evidence (GRADE)**

Ratings	Definitions	Implications
⊕⊕⊕⊕ High	This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low.	This evidence provides a very good basis for making a decision about whether to implement the intervention. Impact evaluation and monitoring of the impact are unlikely to be needed if it is implemented.
⊕⊕⊕◯ Moderate	This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different[4] is moderate.	This evidence provides a good basis for making a decision about whether to implement the intervention. Monitoring of the impact is likely to be needed and impact evaluation may be warranted if it is implemented.
⊕⊕◯◯ Low	This research provides some indication of the likely effect. However, the likelihood that it will be substantially different[4] is high.	This evidence provides some basis for making a decision about whether to implement the intervention. Impact evaluation is likely to be warranted if it is implemented.
⊕◯◯◯ Very low	This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different[4] is very high.	This evidence does not provide a good basis for making a decision about whether to implement the intervention. Impact evaluation is very likely to be warranted if it is implemented.

*Substantially different: large enough difference that it might have an effect on a decision

**The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group began in the year 2000 as an informal collaboration of people with an interest in addressing the shortcomings of present grading systems in health care. The working group has developed a common, sensible and transparent approach to grading quality of evidence and strength of recommendations. Many international organizations have provided input into the development of the approach and have started using it.

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For most recent version of this framework (and additional frameworks): www.decide-collaboration.eu/WP5/Strategies/Framework