WHO/HIV/2014.38

Global Hepatitis Programme

Guideline development for Hepatitis C virus Screening, Care and Treatment in low- and middle-income countries
PICO 5 Treatment (Interferon vs Placebo) – Decision Making Table

Health system and public health evidence to recommendations framework

What is the effectiveness of hepatitis C (HCV) anti-viral treatment compared with no antiviral treatment?

Population: Adults and children with chronic HCV infection

***Intervention*:** Any type of HCV anti-viral therapy

Comparison: No HCV anti-viral therapy

Outcomes: Rates of sustained virological response (SVR), decompensated liver disease, hepatocellular carcinoma, all-cause mortality, treatment-related adverse events leading to discontinuation, quality of life.

Background:

Hepatitis C virus (HCV) infection affects more than 3% of the global population and poses a high economic burden[1,2]. Between 130 and 150 million people are chronically infected, and it is a major cause of hepatocellular carcinoma and liver cirrhosis[3]. Around 350,000 deaths each year occur as a result of infection with HCV. Approved treatments include interferon-alpha (IFN), ribavirin (RBV), and the HCV NS3 protease inhibitors telaprevir and boceprevir.
The purpose of the systematic review was to investigate the utility of treatment versus no treatment for HCV.

	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.	
	Are a large number of people affected?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	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.	

	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*** ☐	Fourteen systematic reviews were included in the final synthesis (Table 1). Six reported data comparing interferon to placebo[4,5,6,7,8,9]. Six combined and compared different types of interferon (standard [IFN] or pegylated interferon [PEG]) to placebo[10,11,12,13,14,15].One review evaluated ribavirin (RBV) monotherapy against placebo[16]. Lond term outcomes are shown in Table 2. **Interferon monotherapy verus placebo** The systematic reviews of effectiveness of IFN monotherapy compared with placebo universally showed that IFN was superior to placebo in achieving SVR. There were inconsistent or statistically non-significant effects of IFN on hepatocellular carcinoma, liver-related morbidity and all-cause mortality. No studies were found that reported quality of life changes with IFN versus placebo. **Interferon and ribavirin dual therapy versus placebo** The systematic reviews of effectiveness of different interferon types (IFN or PEG), in combination with RBV compared with placebo showed clear benefit in achieving SVR (Table 1). There were inconsistent or statistically non-significant effects of PEG/RBV on hepatocellular carcinoma, liver-related morbidity and all-cause mortality. One review reported quality of life changes with PEG versus placebo but without direct statistical comparison. **Ribavirin monotherapy** The systematic review comparing RBV with placebo showed no significant beneficial effect of ribavirin in achieving SVR, reducing all-cause mortality or quality of life. Treatment discontinuation was observed as an adverse event in 5% of the intervention group and there was no improvement in quality of life with ribavirin intervention. **Children** One study reported on the virological outcomes and adverse effects of treatment among children (SVR IFN 45% v. no treatment 9%, p=0.06; OR 8.3 (95% CI 0.6-432.5)[17]. None of the interventions reported differential SVR findings among PWID or HIV-infected individuals as these were most often exclusion criteria for the studies themselves. However, one review among HIV co-infected patients did make other comparisons of different treatment regimens (eg PEG v. IFN) which is addressed a separate systematic review as part of the evidence review process. All reviews of IFN, PEG or RBV versus placebo synthesis randomised controlled trials using appropriate meta-analytical methods, with no significant indirectness or imprecision, so contain high quality evidence according to the GRADE criteria. PICO 5 Treatment or no treatment systematic review	Despite issues notes by the reviews, the quality of evidence was not rated down due to risk of bias.
	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* ☐	***The relative importance or values of the main outcomes of interest:***	
	Are the desirable effects large relative to undesirable effects?	*No* ☐ / *Probably No* ☐ / *Uncertain* ☐ / *Probably Yes* ☒ / *Yes* ☐ / ***Varies*** ☐	While the advantages of SVR were considered to be substantial, the possibility of adverse effects is high, particularly in the context of interferon-containing regimens.	

Outcome	Importance rating	Certainty of the evidence
Failure to achieve SVR		High
Decompensated liver cirrhosis (DCC)		High
Hepatocellular carcinoma (HCC)		Moderate
All-cause mortality		Moderate
Treatment-related adverse events leading to discontinuation		High
Quality of life		Low

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
RESOURCE USE	**Are the resources required small?**	*No* ☒ / *Probably No* ☐ / *Uncertain* ☐ / *Probably Yes* ☐ / *Yes* ☐ / ***Varies*** ☐	***Main resource requirements***	
	Is the incremental cost small relative to the net benefits?	*No* ☒ / *Probably No* ☐ / *Uncertain* ☐ / *Probably Yes* ☐ / *Yes* ☐ / ***Varies*** ☐	Treatment for HCV is costly. Economic modelling data was considered by the Guidelines Committee in the context of people who inject drugs (PWID). In this group, SVR rates were similar to those individuals who do not inject drugs[18]. HCV treatment for PWID is cost-effective in a variety of settings and HCV treatment for PWID may prevent transmission and reduce chronic prevalence[19]	
EQUITY	**What would be the impact on health inequities?**	*Increased* ☐ / *Probably increased* ☐ / *Uncertain* ☒ / *Probably reduced* ☐ / *Reduced* ☐ / ***Varies*** ☐	An intervention targeted at patients most at risk e.g. PWID and prisoners and those exposed to high-risk medical interventions would be highly likely to reduce health inequities.	
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	*No* ☐ / *Probably No* ☐ / *Uncertain* ☐ / *Probably Yes* ☒ / *Yes* ☐ / ***Varies*** ☐		

Resource	Settings
Training	Requires trained medical practitioners/nurse specialists
Supervision and monitoring	Regular monitoring on treatment (the subject of an additional review) Dose adjustments/treatment cessation Medical follow-up
Supplies	Treatment costs Blood testing – for adverse effects and efficacy Promotional materials for health care provider and patients

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
FEASIBILITY	**Is the option feasible to implement?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐	Feasibility is likely to vary substantially in varying clinical settings. Treatment requires clinical infrastructure for follow-up and monitoring on therapy (Technical report on monitoring). Treatment has been successfully rolled out in several low and middle income countries. In particular, Egypt has made treatment available to large numbers of patients.	

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

- All adults and children with chronic HCV infection, including people who inject drugs, should be assessed for antiviral treatment
- We recommend that antiviral medication should be made available for all adults and children with chronic HCV infection

Strong recommendation, moderate quality of evidence

Justification

The evidence that treatment versus no treatment improved outcomes was considered to be moderate although none of the treatment trials of newer medications (pegylated interferon alpha and ribavirin with or without boceprevir or telaprevir) were tested against no treatment.

Implementation considerations

Regular monitoring of patients on treatment is required due to the potential for severe adverse events on therapy.
Costs associated with treating patients are considerable.

Monitoring and evaluation

Regular monitoring of patients on treatment is required due to the potential for severe adverse events on therapy.

Research priorities

It is unlikely that further research comparing treatment versus no treatment will be carried out for ethical reasons.

Evidence profile [title]

Authors: David Hunt, Esther Aspinall, and Hamish Innes

Date: 2013-05-16

Question: What is the effectiveness of hepatitis C (HCV) anti-viral treatment compared with no antiviral treatment?

Settings: Individuals with chronic HCV infection **Bibliography:**

Table 1: Evidence profile: Any IFN alone or with RBV interventions versus no treatment for chronic HCV

Question: Should Any interferon alone or with ribavirin vs Placebo be used for chronic HCV?											
Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With Any interferon alone or with ribavirin		Risk with Placebo	Risk difference with Any interferon alone or with ribavirin (95% CI)
Failure to achieve SVR (Treatment naive) (CRITICAL OUTCOME; assessed with: HCV RNA test 6 months post treatment; Myers 2009[1])											
409 (8 studies) 72 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**	198/200 (99%)	176/209 (84.2%)	**OR 0.15** (0.076 to 0.30)	**990 virological failures per 1000**	**53 fewer virological failures per 1000** (from 23 fewer to 107 fewer)
Failure to achieve SVR (cirrhotics pre or post transplant) (CRITICAL OUTCOME; assessed with: HCV RNA test 6 months post treatment; Xirouchakis 2008)											
279 (4 studies) 72 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**	125/135 (92.6%)	102/144 (70.8%)	**RR 0.71** (0.64 to 0.79)	**926 virological failures per 1000**	**269 fewer virological failures per 1000** (from 194 fewer to 333 fewer)
Treatment discontinuation due to adverse events (CRITICAL OUTCOME; assessed with: treatment stopped; Xirouchakis 2008)											
129 (1 study) 72 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**	0/63 (0%)	13/66 (19.7%)	**RD 0.20** (0.09 to 0.30)	**0 discontinuation per 1000**	**197 more discontinuation per 1000** (from 90 more to 300 more)
Liver-related morbidity during or after treatment (CRITICAL OUTCOME; assessed with: Composite definition; Kimer 2012 [3])											
789 (4 studies) 5-9 years	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	undetected	⊕⊕⊕⊖ **MODERATE**[4] due to imprecision	42/389 (10.8%)	34/400 (8.5%)	**RR 0.73** (0.48 to 1.11)	**108 deaths per 1000**	**29 fewer deaths per 1000** (from 56 fewer to 12 more)
Hepatic decompensation during or after treatment (Cirrhotic patients) (IMPORTANT OUTCOME; assessed with: composite definition; Vezali 2012)											
99 (1 study) 30 months	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	undetected	⊕⊕⊕⊖ **MODERATE**[5] due to imprecision	5/52 (9.6%)	7/47 (14.9%)	**RR 1.55** (0.59 to 3.45)	**96 decompensation per 1000**	**53 more decompensation per 1000** (from 39 fewer to 236 more)
All-cause mortality during or after treatment (Cirrhotic patients) (CRITICAL OUTCOME; assessed with: deaths; Vezali 2012)											
99	no serious	no serious	no serious	serious[5]	undetected	⊕⊕⊕⊖	5/52	10/47	**RR 2.21**	**96 deaths per 1000**	**116 more deaths per 1000**

(1 study) 30 months	risk of bias	inconsistency	indirectness			**MODERATE**[5] due to imprecision	(9.6%)	(21.3%)	(0.69 to 8.25)		(from 30 fewer to 697 more)
All-cause mortality during or after treatment (CRITICAL OUTCOME; assessed with: deaths; Kimer 2012)											
1850 (4 studies) 5-9 years	no serious risk of bias	serious[6]	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁⊖ **MODERATE**[6] due to inconsistency	90/932 (9.7%)	93/918 (10.1%)	**RR 0.81** (0.33 to 2.03)	**97 deaths per 1000**	**18 fewer deaths per 1000** (from 65 fewer to 99 more)
Hepatocellular carcinoma during or after treatment, patients with compensated advanced fibrosis (IMPORTANT OUTCOME; assessed with: HCC detection not specified; Kimer 2012)											
2230 (8 studies) 2-9 years	no serious risk of bias	serious[7]	no serious indirectness	serious[8]	undetected	⨁⨁⊖⊖ **LOW**[7,8] due to inconsistency, imprecision	129/1074 (12%)	81/1156 (7%)	**RR 0.53** (0.34 to 0.81)	**120 diagnoses per 1000**	**56 fewer diagnoses per 1000** (from 23 fewer to 79 fewer)

[1] Myers et al 2009 examined IFN v placebo. Used as a reference point for benefits of treatment compared with no treatment to compare with other outcomes

[2] Review rated primary studies as having significant risk of bias

[3] Liver morbidity defined as variceal bleeding, hepatorenal syndrome, liver failure, spontaneous bacterial peritonitis

[4] Imprecision given composite outcome and short-medium term follow up post treatment

[5] Imprecision given short duration of follow-up for mortality

[6] Inconsistency due to heterogeneity between studies with high I-square

[7] Significant heterogeneity in results

[8] Imprecision in inadequate ascertainment of HCC disease free at study outset

Table 2: Long term outcomes

Quality assessment of Long Term Outcomes							**Summary of Findings**				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no screening (no or failed treatment)	With HCV screening followed by antiviral treatment (PR)		Risk with no screening (no or failed treatment)	Risk difference with HCV screening followed by antiviral treatment (PR) (95% CI)
mortality in HCV population (CRITICAL OUTCOME†; assessed with: death certificate)											
16864 (1 obs. study) 3.8 years§	no serious risk of bias¶	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW**	1126/9434 (11.9%)	409/7434 (5.5%)	**HR 0.7 (0.59 to 0.83)** **	**119 deaths per 1000**	**34 fewer deaths per 1000 (from 19 fewer to 47 fewer)**
hepatocellular carcinoma (CRITICAL OUTCOME; assessed with: imaging, pathology)											
25906 (12 obs. studies) 3.0-8.2 years	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE* due to large effect**	990/16312 (6.1%)	145/9185 (1.6%)	**RR 0.24 (0.18 to 0.31)**	**17 HCC per 1000**	**14 fewer HCC per 1000 (from 12 fewer to 15 fewer)**
QoL associated with SVR-vitality sub-score (CRITICAL OUTCOME; measured with: SF-36; range of scores: 4-24; Better indicated by higher values)											
5978 (7 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ **LOW**	-††	-	-	-	**The mean QoL associated with SVR-vitality sub-score in the intervention groups was 6.6 higher§§ (-)¶¶**

§ Study included the years from 2001 to 2009. The median follow-up period was 3.8 years after final outcome (SVR/NVR) was established. The interquartile range was 2.5 to 5.2 years.
¶ Although adjustment for cirrhosis severity (e.g., CP or MELD score) would be ideal, Backus et al. adjusted for presence of cirrhosis in general and albumin, bilirubin, albumin and platelet count which are valid substitutes for severity of underlying liver disease. Not downgraded.

** The results are for genotype 1 (72% of cohort). Genotype 2: HR 0.64 (CI 0.46, 0.88); genotype 3: 0.51 (CI 0.35, 0.73)

* Rated up due to large relative risk effect: 0.24; 95% CI = 0.18–0.31. Most studies controlled for baseline liver disease severity (for example, presence of cirrhosis) and other important confounders, such as hepatitis B virus infection.

†† Total number of participants = 5,978; distribution between participants and controls not available.

§§ The mean QoL associated with sustained viral response-vitality sub-score in the intervention groups.

¶¶ 95% CI not provided. Effect was reported as significant. Minimally clinically important difference estimated to be 4.2 (range: 3–5). Effect size results: 0.2; effect sizes are classified as small (≤0.2); moderate (0.5); and large (≥0.8)

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References

[1] Georgel, Schuster et al. 2010

[2] El Khoury, Wallace et al. 2012

[3] Coffin, Scott et al. 2012

[4] Malaguarnera, Restuccia et al. (1995)

[5] Carithers and Emerson (1997)

[6] Myers, Regimbeau et al. (2002)

[7] Hu, Doucette et al. (2010)

[8] Koretz, Pleguezuelo et al. (2013)

[9] Tine, Attanasio et al. (2005)

[10] Fabrizi, Ganeshan et al. (2008)

[11] Xirouchakis, Triantos et al. (2008)

[12] Kimer, Dahl et al. (2012)

[13] Iorio, Marchesini et al. (2010)

[14] Hartwell and Shepherd (2009)

[15] Vezali, Aghemo et al. (2010)

[16] Brok, Gluud et al. 2009

[17] Hu, Doucette et al., 2010

[18] Aspinall E, et al. Treatment of Hepatitis C Virus Infection Among People Who Are Actively Injecting Drugs: A Systematic Review and Meta-analysis. *Clinical Infectious Diseases* 2013; In Press.

[19] Martin NK, Vickerman P, Foster GR, Hutchinson SJ, Goldberg DJ, and Hickman M. J Hep 2011; 54:1137-44

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