WHO/HIV/2014.39

World Health Organization

Global Hepatitis Programme

Guideline development for Hepatitis C virus Screening, Care and Treatment in low- and middle-income countries
PICO 6 Treatment (PEG-interferon vs interferon) – Decision Making Table

Health system and public health evidence to recommendations framework

What is the effectiveness of PEG-interferon and ribavirin versus standard interferon and ribavirin for chronic HCV treatment

Population: Adults and children with chronic HCV infection.

Intervention*:* Treatment with pegylated interferon and ribavirin therapy.

Comparison*:* Treatment with standard interferon and ribavirin therapy.

Outcomes: Rates of SVR, decompensated liver disease, hepatocellular carcinoma, all-cause mortality and treatment-related adverse events leading to discontinuation of therapy; quality of life.

Background: The World Health Organization (WHO) estimates that between 130 and 150 million people are chronically infected with hepatitis C (HCV) virus worldwide[1]. People with untreated HCV are at increased risk of liver cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality[2]. According to the most recent guidelines of the European Association for the Study of the Liver (EASL)[3] and the American Association for the Study of Liver Disease (AASLD)[4], the combination of pegylated interferon and ribavirin therapy (with or without the addition of a protease inhibitor in genotype 1 infection) is the approved standard of care for treating individuals with chronic HCV. This review assessed the available evidence to determine whether pegylated interferon is more effective at treating chronic HCV compared to standard interferon with respect to maximising the chance of achieving a sustained virological response (SVR), and reducing morbidity (i.e., decompensated liver disease/hepatocellular carcinoma), mortality and other serious adverse events.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	HCV affects 170 million people around the world; 3% of the world's population.	
	Are a large number of people affected?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	Medical interventions are still associated with transmission of HCV in many countries. A well documented outbreak of HCV infection associated with unsafe injection practice in Egypt resulted in an estimated seroprevalence of up to 25% in at-risk populations (Frank et al, 2000). According to the latest WHO report on blood safety (2011), 39 countries do not routinely screen blood transfusions for blood-borne viruses http://www.who.int/bloodsafety/global_database/en/. Injecting drug use has been reported in 148 countries around the world and is associated with high prevalence rates of HCV http://www.who.int/substance_abuse/facts/en/.	

	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*** ☐	The available evidence indicates that the use of pegylated interferon and ribavirin is more effective at achieving SVR among people with chronic HCV compared to standard interferon and ribavirin, particularly among individuals with non-genotype 1 HCV (Table 1). Overall, there was no significant difference in the rate of study termination due to adverse events among patients administered pegylated versus conventional interferon (both plus ribavirin). Limited data prevented adequate investigation of the rate of liver-related mortality, hepatic decompensation and HCC development among people treated with pegylated versus standard interferon. There is indirect evidence from other systematic reviews that HCV treatment in children and	
	Are the undesirable anticipated effects small?	*No* ☐ *Probably No* ☒ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	What is the overall certainty of this evidence?	*No included studies* ☐ *Very low* ☐ *Low* ☐ *Moderate* ☐ *High* ☒	PWIDs is effective (Table 2). There is a considerable lack of studies examining these outcomes in low-middle income countries. Treatment with pegylated IFN versus conventional IFN given with ribavirin is associated with a substantially higher likelihood of SVR. There is high quality evidence that 126 per 1000 fewer patients fail to attain SVR with pegylated IFN/RBV (661 per 1000 with conventional IFN/RBV). This increase in efficacy was observed in infection with genotype 1 and non-genotype 1, in patients with and without cirrhosis and in treatment naïve and experienced individuals. PICO 6 Treatment PEG versus IFN systematic review	

	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*** ☐	Side effects: 14 fewer cases of HCC per 1000 with pegylated IFN (baseline 21 per 1000); 3 fewer cases of hepatic decompensation (from 17 per 1000) and 5 fewer liver related mortality cases (from 15 per 1000). One more patient per 1000 terminated treatment due to adverse events (from 118 per 1000).	

Outcome	Relative importance	Certainty of the evidence
SVR		High
Decompensated liver cirrhosis (DCC)		Low-moderate
Hepatocellular carcinoma (HCC)		Low
All-cause mortality		Moderate
Adverse events leading to discontinuation		Moderate
Quality of life		No evidence

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
RESOURCE USE	**Are the resources required small?**	*No* ☒ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐	***Main resource requirements*** **Resource** / **Settings** *Training* — Doctors/specialist nurses *Supervision and monitoring* — Treatment given for 1 year and fol months thereafter *Supplies* — IFN/RBV/DAA therapy	
	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[5]. HCV treatment for PWID is cost-effective in a variety of settings and HCV treatment for PWID may prevent transmission and reduce chronic prevalence[6]. In Egypt, the cost of IFN is approximately $2000 (USD). Modelling has shown that treatment of patients with compensated F4 disease is cost-effective in this context[7].	
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. people of lower socio-economic status and PWID and prisoners is likely to improve health inequities.	

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
ACCEPTABILITY	**Is the option acceptable to key stakeholders ?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐	-	
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 ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts	We recommend the option ☒

Recommendation	Pegylated interferon in combination with ribavirin is recommended for the treatment of chronic HCV infection rather than standard non-pegylated interferon with ribavirin. Strong recommendation, moderate quality of evidence.
Justification	The evidence that pegylated interferon is superior to standard interferon at producing a sustained virological response to treatment is high.
Implementation considerations	The cost of pegylated interferon may be higher and may not be available in some countries.
Monitoring and evaluation	Regular monitoring of patients on treatment is required due to the potential for severe adverse events on therapy.
Research priorities	There is a lack of research examining the safety and efficacy of pegylated versus standard interferon (both plus ribavirin) in low-middle income countries.

Evidence profile [title]

Authors: David Hunt, Esther Aspinall, and Hamish Innes

Date: 2013-05-16

Question: What is the effectiveness of PEG-interferon and ribavirin versus standard interferon and ribavirin for chronic HCV treatment

Settings: Individuals with chronic HCV infection

Bibliography: [Citation text]

Table 1: GRADE summary of findings

Question: Should pegylated interferon and ribavirin vs standard interferon and ribavirin be used for 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 Standard interferon and ribavirin	With Pegylated interferon and ribavirin		Risk with Standard interferon and ribavirin	Risk difference with Pegylated interferon and ribavirin (95% CI)
Failure to achieve sustained virological response (CRITICAL OUTCOME)											
6350 (25 studies) 72 weeks	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**[1]	1889/2858 (66.1%)	1855/3492 (53.1%)	**RR 0.81** (0.76 to 0.86)	**661 per 1000**	**126 fewer per 1000** (from 93 fewer to 159 fewer)
Terminated study due to adverse events (CRITICAL OUTCOME)											
5013 (16 studies) 72 weeks	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to inconsistency	264/2231 (11.8%)	340/2782 (12.2%)	**OR 1.01** (0.79 to 1.29)	**118 per 1000**	**1 more per 1000** (from 22 fewer to 29 more)
All-cause mortality during study (CRITICAL OUTCOME)											
1402 (5 studies) 72 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	undetected	⊕⊕⊕⊖ **MODERATE**[3] due to imprecision	9/701 (1.3%)	11/701 (1.6%)	**OR 1.26** (0.52 to 3.07)	**13 per 1000**	**3 more per 1000** (from 6 fewer to 26 more)
Liver-related mortality during study (CRITICAL OUTCOME)											
533 (2 studies) 72 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	undetected	⊕⊕⊕⊖ **MODERATE**[4] due to imprecision	4/268 (1.5%)	2/265 (0.75%)	**OR 0.63** (0.12 to 3.27)	**15 per 1000**	**5 fewer per 1000** (from 13 fewer to 32 more)

Hepatic decompensation during study (IMPORTANT OUTCOME)											
694 (2 studies) 72 weeks	serious[5]	no serious inconsistency	no serious indirectness	serious[4]	undetected	⊕⊕⊖⊖ **LOW**[4,5] due to risk of bias, imprecision	6/346 (1.7%)	5/348 (1.4%)	**OR 0.84** (0.19 to 3.74)	**17 per 1000**	**3 fewer per 1000** (from 14 fewer to 45 more)
Development of hepatocellular carcinoma during study (IMPORTANT OUTCOME)											
96 (1 study) 72 weeks	no serious risk of bias[6]	serious[6]	no serious indirectness	very serious[6]	undetected	⊕⊖⊖⊖ **VERY LOW**[6] due to inconsistency, imprecision	1/48 (2.1%)	0/48 (0%)	**OR 0.33** (0.01 to 8.22)	**21 HCC per 1000**	**14 fewer HCC per 1000** (from 21 fewer to 128 more)

[1] Most information is from studies at low risk of bias. However, some studies were at bias associated with sequence generation and allocation concealment (e.g., the randomization process was not always explicitly described (see Simin et al., 2007, and Kim et al., 2007))

[2] There is significant heterogeneity between studies in findings regarding patients administered PEG-IFN + RBV vs. IFN-RBV.

[3] Few events, wide confidence interval.

[4] Some imprecision due to few events.

[5] These two studies only involve HCV/HIV coinfected participants (i.e., results cannot be generalised to individuals with chronic HCV without HIV).

[6] One study of Saudi Arabian patients (with a focus on those with HCV genotype 4 and a relatively small sample size) limits the representativeness of findings.

Table 2: Indirect evidence from systematic reviews of HCV treatment in Children and PWID

Study, methods	No of studies (numbers and population)	Intervention Outcomes	Summary of primary findings (95% confidence interval)	Review conclusions
Druyts *et al. (*2013) Systematic review Cochrane/PRISMA compliant	1 RCT, 7 non-randomised trials (n=438, 3-18 year children/adolescents)	PEG+RBV for all patients Measured SVR, treatment discontinuation due to AE	Among children: • SVR: 58% (95%CI 53-64) • Treatment discontinuation due to AE: 4% (1-7%)	Treatment is effective and safe in treating children and adolescents with HCV
Aspinall *et al.* (2013) Systematic review Cochrane/PRISMA compliant	6 observational studies (n=314 PWID, 45% active PWID in last month)	PEG+RBV for all patients Measured SVR, adherence, treatment discontinuation (all-cause)	Among PWID: • SVR 61% (51-72%) • Adherence 82% (74-89%) • Treatment discontinuation (all-cause, not AE specific) 22% (16-27%)	Treatment among active PWID has a comparable SVR and adherence rates among studies to former or non-PWID.

[1] World Health Organization 2012

[2] [2]

[3] EASL guidelines

[4] AASLD

[5] 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.

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

[7] D'Amico et al 2006

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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