WHO/HIV/2014.40

Global Hepatitis Programme

Guideline development for Hepatitis C virus Screening, Care and Treatment in low- and middle-income countries
PICO 7 Treatment (pegylated interferon and ribavirin vs. DAAs) – Decision Making Table

Health system and public health evidence to recommendations framework

Among people with chronic HCV, is treatment containing direct acting antiviral agents (Boceprevir or Telaprevir) more effective than treatment with pegylated interferon and ribavirin alone?

Population: Adults and children with chronic HCV infection (genotype 1)

Intervention*:* Direct-acting antiviral (DAA) therapy (Boceprevir or Telaprevir) in addition to pegylated interferon and ribavirin therapy

Comparison*:* Pegylated interferon and ribavirin therapy alone

Outcomes: Number achieving sustained virological response; number of cases of decompensated liver disease/hepatocellular carcinoma/all-cause mortality; treatment-related serious adverse events leading to discontinuation of therapy; and quality of life.

Background: At the time of writing, five drugs are licensed for the treatment of HCV; standard interferon alpha, pegylated interferon alpha, ribavirin (RBV) and the protease inhibitors (PIs) boceprevir and telaprevir. However, over the coming years, the spectrum of treatments available for HCV infection will expand following an intense research effort by academic institutions and pharmaceutical companies. This is likely to result in a substantial improvement in treatment success rates. Several factors will limit the success of treatment, the most significant of which are cost, access to treatment, toxicity profile, drug-drug interactions and efficacy related to the emergence of resistance mutations. New treatments are still urgently needed for HCV that are more efficacious, less toxic and ideally less expensive, particularly in resource-limited settings. Encouragingly, further treatments for HCV are emerging rapidly and several are in advanced stages of clinical development. The majority of these agents are targeted against viral proteins and are collectively termed “direct-acting antiviral” compounds (DAAs). The most promising of these include new NS3 protease inhibitors, some of which have pangenotypic activity, inhibitors of the NS5A replication complex and inhibitors of the viral RNA-dependent polymerase. The future of HCV treatment is likely to be improved by the availability of DAAs to be used in combination without the need for IFN – this has major future implications for low and middle income countries. However, in this systematic review, treatment with pegylated interferon and ribavirin with or without DAA therapy with boceprevir or telaprevir was considered.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	Chronic HCV affects 130-150 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[1]. 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*** ☐	Data were considered for FDA approved direct acting antivirals only. A systematic review of currently licensed DAAs (telaprevir and boceprevir) given with IFN/RBV (triple therapy) versus IFN/RBV alone for patients with chronic genotype 1 HCV showed high quality evidence that DAA/IFN/RBV would result in 315 per 1000 fewer virological failures compared to IFN/RBV given alone (Grade Table 1; baseline failure rate 643 failures per 1000). Triple therapy is effective in patients with mild and advanced liver fibrosis. PICO 7 Treatment DAAs systematic review	
	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* ☐	Triple antiviral therapy with pegylated interferon, ribavirin and telaprevir or boceprevir is associated with a substantial increase in SVR rate in patients infected with genotype 1 HCV. The CUPIC study[2] revealed a higher risk of side effects in treatment-experienced patients with compensated cirrhosis; 40% of patients developed a serious adverse event and 11.7% had to cease therapy.	

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
			The relative importance or values of the main outcomes of interest:	
			Outcome / **Relative importance** / **Certainty of the evidence** SVR — Moderate All-cause mortality — High Serious adverse events leading to discontinuation — Moderate	
	Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐	As above, based on the systematic review evidence, 315 fewer virological failures/1000 are anticipated with DAA/IFN/RBV therapy. However, 41 more cases of grade 3 or 4 anaemia (defined as Hb<8.5 g/dl) were anticipated (baseline of 22 per 1000 with IFN/RBV). Grade 3 or 4 neutropenia (defined as a neutrophil count <750/mm3) was estimated to occur at a baseline rate of 174 per 1000 with an additional 106 cases per 1000 with DAA-based therapy. Discontinuation rates was estimated to be similar in patients treated with IFN/RBV (95 per 1000) versus IFN/RBV/DAA therapy (17 more discontinuations per 1000).	

	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 follow up for months thereafter	

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
			Supplies IFN/RBV/DAA therapy	
	Is the incremental cost small relative to the net benefits?	*No* ☐ *Probably No* ☐ *Uncertain* ☒ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐	For patients with mild disease, the incremental cost was considered to be small relative to the net benefit. In high income settigns, an assesment by NICE in the UK evaluated DAAs as being cost-effective. For more advanced disease, due to the increased risk of severe adverse events (as discussed above), this was considered to be less certain and would be likely to require increased monitoring, particularly for evidence of anaemia. The availability of enhanced monitoring is likely to be context spoecific in low and middle income countries.	
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.	
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	The option was considered to be likely to be acceptable to key stakeholders as inclusion of a DAA is associated with a substantially higher chance of SVR. No difficulties were anticipated in relation to unforeseen consequences or cultural contexts. Some difficulty in obtaining high fat meals for cultural reasons for example during Ramadan was but it was felt likely that stakeholders would approve use in the context of medical illness.	

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
FEASIBILITY	**Is the option feasible to implement?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☒	Feasibility will be variable in different infrastructure and healthcare service settings. While DAA therapy is associated with a marked increase in SVR rate, it is also associated with an increase in the incidence of side effects. The severity of undesirable consequences in settings where monitoring for anaemia (worse in the context of DAAs versus dual therapy) or severe rash (telaprevir) needs to be considered by individual countries. Treatment should be implemented only in settings where the appropriate infrastructure exists. In low income countries, this problem is most pronounced. In countries that can afford triple therapy, it was considered that it should be feasible also to fund appropriate monitoring.	

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	Treatment with currently approved direct-acting antivirals (telaprevir or boceprevir), given in combination with pegylated interferon and ribavirin is suggested for genotype 1 chronic hepatitis C infection rather than pegylated interferon and ribavirin alone Conditional recommendation, moderate quality of evidence		
Justification	The evidence showing that inclusion of a protease inhibitor (boceprevir or telaprevir) to pegylated interferon and ribavirin regimen increases the likelihood of a sustained virological response is strong for patients with chronic HCV infection (genotype 1). However, there is an increase in adverse events with triple therapy and monitoring patients more regularly may be challenging in low and middle income settings.		
Implementation considerations	Triple therapy should be given in specialist centres for side effects where appropriate monitoring can be carried out. DAAs given without IFN are likely to be available in 2014-15. This guidance is likely to be updated when further studies become available.		
Monitoring and evaluation	Triple therapy should be given in specialist centres for side effects where appropriate monitoring can be carried out. Further detail is given in the Technical Report on Monitoring section.		
Research priorities	Improvements in virological response may lead to improvements in liver related morbidity and mortality however there are no direct data available from these studies to make definite conclusions about longer term outcomes. The significance of severe neutropenia on HCV treatment remains unclear.		

Evidence profile [title]

Authors: David Hunt, Esther Aspinall, and Hamish Innes
Date: 2013-05-16
Question: Among people with chronic HCV, is treatment containing direct acting antiviral agents more effective than treatment with pegylated interferon and ribavirin alone?
Settings: Individuals with chronic HCV infection
Bibliography: [Citation text]

Table 1: Evidence Profile – DAA+PR versus PR in chronic HCV infection

Question: Should direct acting antiviral therapy with PEG/RBV vs PEG/RBV be used for chronic HCV infection?											
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 PEG/RBV	**With Direct acting antiviral therapy with PEG/RBV**		**Risk with PEG/RBV**	**Risk difference with Direct acting antiviral therapy with PEG/RBV** (95% CI)
Failure to achieve SVR (CRITICAL OUTCOME; assessed with: HCV RNA test 6 months post treatment)											
3305 (4 studies) 72 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁⨁ **HIGH**	602/936 (64.3%)	825/2369 (34.8%)	**RR 0.51** (0.47 to 0.55)	**643 virological failures per 1000**	**315 fewer virological failures per 1000** (from 289 fewer to 341 fewer)
AE (Grade 3 or 4 anaemia) (IMPORTANT OUTCOME; assessed with: Hb <8.5g/dl during treatment)											
3250 (4 studies) 72 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁⨁ **HIGH**	21/936 (2.2%)	170/2314 (7.3%)	**RR 2.84** (1.78 to 4.54)	**22 anaemia per 1000**	**41 more anaemia per 1000** (from 18 more to 79 more)
AE (Grade 3 or 4 neutropenia) (IMPORTANT OUTCOME; assessed with: Neutrophil count <750/mm3 during therapy)											
2162 (3 studies) 72 weeks	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	undetected	⨁⨁⨁⊖ **MODERATE**[1] due to indirectness	100/575 (17.4%)	432/1587 (27.2%)	**RR 1.61** (1.29 to 2)	**174 neutropenia per 1000**	**106 more neutropenia per 1000** (from 50 more to 174 more)

Adverse event leading to treatment discontinuation (CRITICAL OUTCOME)											
3250 (4 studies) 72 weeks	no serious risk of bias	no serious inconsistency[2]	no serious indirectness	serious[3]	undetected	⨁⨁⨁⊖ **MODERATE**[2,3] due to imprecision	89/936 (9.5%)	239/2314 (10.3%)	**RR 1.18** (0.93 to 1.49)	**95 discontinuation per 1000**	**17 more discontinuation per 1000** (from 7 fewer to 47 more)
Mortality during study (CRITICAL OUTCOME)											
2588 (3 studies) 72 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[4]	undetected	⨁⨁⨁⨁ **HIGH**[4]	5/804 (0.62%)	6/1784 (0.34%)	**RR 0.51** (0.15 to 1.76)	**6 deaths per 1000**	**3 fewer deaths per 1000** (from 5 fewer to 5 more)

[1] Neutropenia not clearly related to infections or changes in management

[2] Inconsistency in finding due to imprecision in effect, so this outcome was only rated down for imprecision

[3] Imprecision due to definitions of adverse events and relationship to outcome

[4] This outcome was not marked down for imprecision despite only a few events because of the large sample size

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References

[1] Frank et al, 2000

[2] Hézode C, Fontaine H, Dorival C, Larrey D, Zoulim F, Canva V, de Ledinghen V, Poynard T, Samuel D, Bourlière M, Zarski JP, Raabe JJ, Alric L, Marcellin P, Riachi G, Bernard PH, Loustaud-Ratti V, Métivier S, Tran A, Serfaty L, Abergel A, Causse X, Di Martino V, Guyader D, Lucidarme D, Grando-Lemaire V, Hillon P, Feray C, Dao T, Cacoub P, Rosa I, Attali P, Petrov-Sanchez V, Barthe Y, Pawlotsky JM, Pol S, Carrat F, Bronowicki JP; CUPIC Study Group. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. J Hepatol. 2013 May 10. doi:pii: S0168-8278(13)00290-0.

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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