WHO/HIV/2014.41

World Health Organization

Global Hepatitis Programme

Guideline development for Hepatitis C virus Screening, Care and Treatment in low- and middle-income countries
PICO 7 Treatment (Sofosbuvir) – Decision Making Table

Evidence to recommendation framework

Should sofosbuvir be used to treat chronic hepatitis C?

Problem: HCV genotype 1, 2, 3, or 4 infection
Option: sofosbuvir + ribavirin (+/- peg-INF)
Comparison: placebo (interferon intolerant);
or peg-INF + ribavirin
Setting: ambulatory care
Perspective: WHO

Background: [Background]

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
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.	

Problem: HCV genotype 1, 2, 3, or 4 infection ***Option:*** SOF + RBV (+/- peg-INF) ***Comparison:*** *placebo;* peg-INF+RBV ***Setting:*** ambulatory care

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Moderate* ☐ | *High* ☒		
Is there important uncertainty about how much people value the main 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* ☐		
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐		
Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐		

Summary of findings: GT 1 and 4; 12 weeks: *SOF+RBV+peg-INF vs. peg-INF (historical controls)*

Outcome	Without SOF (per 1000)	With SOF (per 1000)	Difference (per 1000 (95%CI)	Relative effect (RR) (95%CI)	Certainty of the evidence (GRADE)
Failure of SVR	350	97	**253 less (from 216 to 279 less)**	**RR 0.3** (estimate)	HIGH (large effect and dose-response)
SAE: treatment discontinuation	42	24	**18 fewer (36 fewer to 56 more)**	**RR 0.57** (0.14 to 2.33)	MODERATE due to imprecision

Summary of findings: GT 2, 12 weeks: *SOF+RBV vs. placebo*

Outcome	Without SOF (per 1000)	With SOF (per 1000)	Difference (per 1000 (95%CI)	Relative effect (RR) (95%CI)	Certainty of the evidence (GRADE)
Failure of SVR	1000	82	**918 less (from 878 to 944 less)**	**RR <0.1** (estimate)	HIGH (large effect and dose-response)
SAE: treatment discontinuation	42	24	**18 fewer (36 fewer to 56 more)**	**RR 0.57** (0.14 to 2.33)	MODERATE due to imprecision

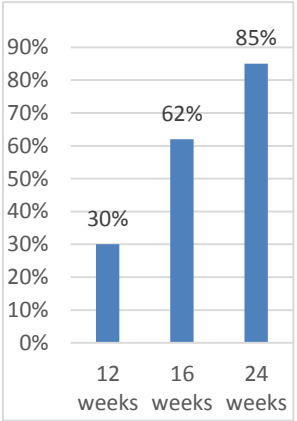
Summary of findings: GT 3, 24 weeks: *SOF+RBV vs. placebo (historical controls)*

Outcome	Without SOF (per 1000)	With SOF (per 1000)	Difference (per 1000 (95%CI)	Relative effect (RR) (95%CI)	Certainty of the evidence (GRADE)
Failure of SVR	1000	150	**850 less (from 800 to 878 less)**	**RR <0.2** (estimate)	HIGH (large effect and dose-response)
SAE: treatment discontinuation	42	24	**18 fewer (36 fewer to 56 more)**	**RR 0.57** (0.14 to 2.33)	MODERATE due to imprecision

Link to detailed evidence profile

HIV co-infected populations were pooled with non-HIV co-infected populations for genotypes, 1, 2, 3, and 4.

Example of cumulative dose-response-gradient (seen for SOF in genotype 3 infection, treatment experienced):



Date: **2013-12-02**

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	**Are the resources required small?**	*No* ☐ *Probably No* ☐ *Uncertain* ☒ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐	At the time of deliberations, detailed pricing information was unavailable for countries covered in this guideline.	
	Is the incremental cost small relative to the net benefits?	*No* ☐ *Probably No* ☐ *Uncertain* ☒ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐		
EQUITY	**What would be the impact on health inequities?**	*Increased* ☐ *Probably increased* ☐ *Uncertain* ☒ *Probably reduced* ☐ *Reduced* ☐ ***Varies*** ☐		
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*** ☐	No refrigeration necessary; once daily dosing	

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 offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)	Sofosbuvir, given in combination with ribavirin (+/- pegylated interferon) is recommended in genotype 1, 2, 3 and 4 HCV infection (non-HIV co-infected and HIV co-infected populations) rather than pegylated interferon and ribavirin alone or no treatment (interferon intolerant). Strong recommendation, high quality of evidence Note: This recommendation was made without explicit resource use considerations as detailed pricing information was unavailable for countries covered in this guideline at the time of deliberations.
Justification	[to follow]
Subgroup considerations	Treatment duration: in combination with pegylated interferon: 12 weeks; without peg-INF: 12 weeks (genotype 2 only); 24 weeks (genotype 1 or 3).
Implementation considerations	[to follow]
Monitoring and evaluation	[to follow]
Research priorities	[to follow]

Author(s): YFY
Date: 2013-12-09

Question 1a: Should sofosbuvir/peg-INF/ribavirin for 12 weeks vs. peg-INF/ribavirin be used for HCV GT1/4 (treatment naïve)?

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-INF/ribavirin	**With Sofosbuvir/peg-INF/ribavirin**		**Risk with Peg-INF/ribavirin**	**Risk difference with Sofosbuvir/peg-INF/ribavirin** (95% CI)
failure of SVR (CRITICAL OUTCOME)											
616 (2 single arm cohorts without controls)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**[3,4] due to large effect, dose-response gradient	35%[1]	34/350 (9.7% pooled)	**RR 0.3**[2]	**350 SVR failures per 1000**[1]	**253 fewer SVR failures per 1000** (from 216 to 279 fewer)
Sofosbuvir adverse event related treatment discontinuation (IMPORTANT OUTCOME)											
278 (1 placebo controlled RCT[7])	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	undetected	⊕⊕⊕⊖ **MODERATE**[5] due to imprecision			**RR 0.57** [7] (0.14 to 2.33)	**42 per 1000**[6]	**18 fewer per 1000** (from 36 fewer to 56 more)

[1] Assumed SVR failure rate based on historical controls. A 65% SVR rate, although observed in clinical trials, is likely to be on the highest end plausible.
[2] Estimated RR based on assumed SVR failure rate of SVR (historical controls)
[3] Large effect (likely more than 70% RRR of SVR failure) based on assumption of a historically observed SVR rate of max. 65% for peg-INF/RB in treatment naïve patients (historical controls)
[4] Pronounced cumulative dose-response gradient observed in difficult to treat genotypes, such as genotype 3.
[5] Wide confidence interval, few events.
[6] 1.5% - 9% discontinuation rate observed in the studies included
[7] No comparative data available - single arm studies. RR estimate for SOF related treatment discontinuation taken from POSITRON study (SOF/RBV vs. placebo)

Question 2a: Should sofosbuvir/ribavirin for 24 weeks vs. no treatment be used for HCV GT1 (treatment naïve, interferon intolerant)?

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 No treatment	**With Sofosbuvir/ribavirin**		**Risk with No treatment**	**Risk difference with Sofosbuvir/ribavirin** (95% CI)
failure of SVR (CRITICAL OUTCOME)											
278 (2 single arm cohorts without controls)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**[3,4] due to very large effect, dose-response gradient	100%[1]	35/139 (25.5% pooled)	**RR <0.1**[2]	**1000 SVR failures per 1000**[1]	**745 fewer SVR failures per 1000** (from 660 to 808 fewer)
Sofosbuvir adverse event related treatment discontinuation (IMPORTANT OUTCOME)											
278 (1 placebo controlled RCT[7])	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	undetected	⊕⊕⊕⊖ **MODERATE**[5] due to imprecision	3/71 (4.2%)[6]	5/207 (2.4%)	**RR 0.57** (0.14 to 2.33)	**42 per 1000**[6]	**18 fewer per 1000** (from 36 fewer to 56 more)

[1] Assumed SVR failure rate based on placebo controls of 1 study.
[2] Estimated RR based on assumed SVR failure rate of SVR (placebo control rate from 1 study)
[3] Large effect as the placebo control arm (one study only) showed an expected SVR rate of 0/78.
[4] Pronounced cumulative dose-response gradient observed in difficult to treat genotypes, such as genotype 3.
[5] Wide confidence interval, few events.
[6] 0% - 9% discontinuation rate observed in the studies included
[7] Most studies were single arm studies. Estimate for SOF related treatment discontinuation taken from POSITRON study (SOF/RBV vs. placebo).

Question 3: Should sofosbuvir/ribavirin for 12 weeks vs. no treatment be used for HCV GT2 (treatment naive/experienced)?

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 No treatment	**With Sofosbuvir/ribavirin**		**Risk with No treatment**	**Risk difference with Sofosbuvir/ribavirin** (95% CI)
failure of SVR (CRITICAL OUTCOME)											
628 (5 single arm cohorts included)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁⨁ **HIGH**[3,4] due to very large effect, dose-response gradient	100%[1]	23/314 (8.2% pooled)	**RR <0.1**[2]	**1000 SVR failures per 1000**[1]	**918 fewer SVR failures per 1000** (from 878 to 944 fewer)
Sofosbuvir adverse event related treatment discontinuation (IMPORTANT OUTCOME)											
278 (1 placebo controlled RCT[7])	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	undetected	⨁⨁⨁⨀ **MODERATE**[5] due to imprecision	3/71 (4.2%)[6]	5/207 (2.4%)	**RR 0.57** (0.14 to 2.33)	**42 per 1000**[6]	**18 fewer per 1000** (from 36 fewer to 56 more)

[1] Assumed SVR failure rate based on placebo controls of 1 study.
[2] Estimated RR based on assumed SVR failure rate of SVR (placebo control rate from 1 study)
[3] Large effect as the placebo control arm (one study only) showed an expected SVR rate of 0/78.
[4] Pronounced cumulative dose-response gradient observed in difficult to treat genotypes, such as genotype 3.
[5] Wide confidence interval, few events.
[6] 1% - 3% discontinuation rate observed in the studies included
[7] Most studies were single arm studies. Estimate for SOF related treatment discontinuation taken from POSITRON study (SOF/RBV vs. placebo).

Question 4a: Should sofosbuvir/ribavirin for 12 weeks vs. not treatment be used for HCV GT3 (treatment naive/experienced)?

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 Not treatment	**With Sofosbuvir/ribavirin for 12 weeks**		**Risk with Not treatment**	**Risk difference with Sofosbuvir/ribavirin for 12 weeks** (95% CI)
failure of SVR (CRITICAL OUTCOME)											
774 (4 single arm cohorts included)	no serious risk of bias	serious inconsistency[8]	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁⨁ **HIGH**[3,4] due to large effect, dose-response gradient	100%[1]	178/387 (51.3% pooled)	**RR <0.5**[2]	**1000 SVR failures per 1000**[1]	**487 fewer SVR failures per 1000** (from 433 to 536 fewer)
Sofosbuvir adverse event related treatment discontinuation (IMPORTANT OUTCOME)											
278 (1 placebo controlled RCT[7])	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	undetected	⨁⨁⨁⊖ **MODERATE**[5] due to imprecision	3/71 (4.2%)[6]	5/207 (2.4%)	**RR 0.57** (0.14 to 2.33)	**42 per 1000**[6]	**18 fewer per 1000** (from 36 fewer to 56 more)

[1] Assumed SVR failure rate based on placebo controls of 1 study.
[2] Estimated RR based on assumed SVR failure rate of SVR (placebo control rate from 1 study)
[3] Large effect as the placebo control arm (one study only) showed an expected SVR rate of 0/78.
[4] Pronounced cumulative dose-response gradient observed in difficult to treat genotypes, such as genotype 3.
[5] Wide confidence interval, few events.
[6] 1% - 3% discontinuation rate observed in the studies included
[7] Most studies were single arm studies. Estimate for SOF related treatment discontinuation taken from POSITRON study (SOF/RBV vs. placebo).
[8] Inconsistency observed (I squared 89%) – this was caused by a dramatic drop in SVR to ~30% in a study with treatment experienced patients with genotype 3 (not observed in studies with sufficient treatment length – see 24 weeks data in genotype 3). Not rated down.

Question 4b: Should sofosbuvir/ribavirin for 24 weeks vs. no treatment be used for HCV GT3 (treatment naive/experienced)?

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 No treatment	**With Sofosbuvir/ribavirin for 24 weeks**		**Risk with No treatment**	**Risk difference with Sofosbuvir/ribavirin for 24 weeks** (95% CI)
failure of SVR (CRITICAL OUTCOME)											
524 (2 single arm cohorts included)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**[3,4] due to very large effect, dose-response gradient	100%[1]	39/262 (15.0% pooled)	**RR <0.2**[2]	**1000 SVR failures per 1000**[1]	**850 fewer SVR failures per 1000** (from 800 to 878 fewer)
SOF related treatment discontinuation (IMPORTANT OUTCOME)											
278 (1 placebo controlled RCT[7])	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	undetected	⊕⊕⊕⊖ **MODERATE**[5] due to imprecision	3/71 (4.2%)[6]	5/207 (2.4%)	**RR 0.57** (0.14 to 2.33)	**42 per 1000**[b]	**18 fewer per 1000** (from 36 fewer to 56 more)

[1] Assumed SVR failure rate based on placebo controls of 1 study.
[2] Estimated RR based on assumed SVR failure rate of SVR (placebo control rate from 1 study)
[3] Large effect as the placebo control arm (one study only) showed an expected SVR rate of 0/78.
[4] Pronounced cumulative dose-response gradient observed in difficult to treat genotypes, such as genotype 3.
[5] Wide confidence interval, few events.
[6] 1% - 3% discontinuation rate observed in the studies included
[7] Most studies were single arm studies. Estimate for SOF related treatment discontinuation taken from POSITRON study (SOF/RBV vs. placebo).

Question 4c: Should sofosbuvir/ribavirin/peg-INF for 12 weeks vs sofosbuvir/ribavirin for 24 weeks be used for HCV GT3 (treatment experienced + cirrhosis)?

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 Sofosbuvir/ribavirin for 24 weeks	**With Sofosbuvir/ribavirin peg-INF for 12 weeks**		**Risk with Sofosbuvir/ribavirin for 24 weeks**	**Risk difference with Sofosbuvir/ribavirin/peg-INF for 12 weeks** (95% CI)
failure of SVR (CRITICAL OUTCOME)											
69 (2 single arm studies – indirect comparison)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4] imprecision	undetected	⨁⊖⊖⊖ **VERY LOW**[4] due to imprecision and indirect comparison	18/45 (40%)[1]	2/12 (16.7%)[2]	**RR 0.42**[3]	**400 SVR failures per 1000**[1]	**233 fewer SVR failures per 1000**
treatment discontinuations (IMPORTANT OUTCOME)											
297 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4] imprecision	undetected	⨁⊖⊖⊖ **VERY LOW**[4] due to imprecision and indirect comparison	1/250 (0.4%)	1/47 (2.1%)	**RR 5**[3]	**4 per 1000**	**16 more per 1000**

[1] Event rate from VALENCE study (GT3, subgroup of treatment experience patients with cirrhosis)
[2] Event rate from LONESTAR-2 (GT3, subgroup of treatment experience patients with cirrhosis)
[3] Estimate
[4] Few events, small sample size
(Return)

References

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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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