South African National Department of Health
Brief Report of Rapid Review
Component: Tertiary and Quaternary Level

TITLE: Sofosfobuvir/velpatasvir for management of chronic viral hepatitis C

Date: July 2023

Key findings

- The direct acting antiviral, sofosbuvir-velpatasvir has been shown to be effective across all genotypes of hepatitis C.[9,10,Error! Bookmark not defined.]
- Sofosbuvir-velpatasvir achieved sustained virological response (SVR12) rates of 94.2% (95% CI 90.7 to 97.7%, *P* < .001) in 1277 patients.[9]
- Virologic response rates for historic theoretical standard of care (Pegylated interferon and ribavirin) reported to be 54% to 63%[3]
- Sofosbuvir-velpatasvir was demonstrated to be cost-saving as compared to pegylated interferon and ribavirin. Per patient treatment costs were decreased by R77 534, while per patient QALYs increased by 0.50 QALYs over 20 years. The ICER was calculated at –R155 232, with a decreased budget impact of R63 million over 30 years.
- The use of pegylated interferon plus ribavirin has not been previously recommended on the essential medicines list, and not routinely used for the management of chronic viral hepatitis C due to a lack of affordability. This was accounted for in a sensitivity analysis of the economic analysis where the proportion of patients eligible for pegylated interferon and ribavirin therapy who actually received treatment ranged from 0% to 100%. The sofosbuvir-velpatasvir ± ribavirin intervention was cost-effective and cost-saving in the large majority of simulations conducted (ICER calculated as –R23 068, and a decreased budget impact of R33 million over 30 years).

TERTIARY AND QUATERNARY EXPERT REVIEW COMMITTEE RECOMMENDATION:

	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
Type of recommendation					X

It is recommended that sofosbuvir-velpatasvir should be added to the Essential Medicines List and Standard Treatment Guidelines for the management of chronic Hepatitis C infections.

Rationale: Sofosbuvir-velpatasvir achieves a favourable sustained virological response which is greater than historic theoretical standard of care (pegylated interferon and ribavirin) and has been shown to be a cost saving option even if in the context of limited or no pegylated interferon plus ribavirin use.

Level of Evidence: *I (systematic review and randomised controlled trials)*
Review Indicator: *New evidence of efficacy and safety (particularly local evidence), pricing changes*
(Refer to appendix 1 for the evidence to decision framework)

BACKGROUND

South Africa has an estimated prevalence of hepatitis C ranging between 0.3-1%, equating to approximately 600 000 patients that require treatment.[1] Complications of hepatitis C infection include chronic hepatitis and the development of cirrhosis, conditions associated with increased morbidity and mortality if left untreated.[2] Traditional treatment options in South Africa include the use of antiviral agents such as ribavirin and pegylated interferon 2a, which result in sustained virological response rates (SVR) of 54 to 63%.[3] By contrast, current global therapeutic strategies have largely incorporated the use of direct-acting hepatitis C antiviral agents (DAAs) since 2014.[2] Sofosbuvir and velpatasvir prevent RNA replication by inhibition of the NS5B and NS5A proteins respectively.[4] This drug combination has also been included in the World Health Organization (WHO) Model List of Essential Medicines.[5] The use of DAA's such as sofosbuvir and velpatasvir have resulted in SVRs over 90-95% for the large majority of patients, including those with advanced stages of liver cirrhosis.[2] These agents appear to have improved safety and ultimately reduce requirements for liver transplantation and mortality.[6] Improvements in quality of life among patients receiving this new class of agents have been demonstrated.[7] Additionally, these agents have similar efficacy regardless of the hepatitis C virus (HCV) genotype, thus eliminating the need for tailored therapy according to genotype and therefore allowing pan-genotypic treatment regimens to be developed.[2]

The National Department of Health Viral Hepatitis Guidelines have recommended inclusion of DAA's for management of patients with viral hepatitis as part of their step-wise role out plan.[8] A previous review was conducted on DAAs (particularly sofosbuvir-daclatasvir) for viral hepatitis (NEMLC June 2017), however no decision could be taken as no DAA's were registered in South Africa at the time. Sofosbuvir and velpatasvir has recently been registered in South Africa, allowing for consideration for inclusion as part of the Essential Medicines List for the Management of viral hepatitis.

Two DAA's have been registered in South Africa, (1) sofosbuvir-velpatasvir and (2) sofosbuvir-ledipasvir. Sofosbuvir-velpatasvir was selected for review as it covers all genotypes, whereas sofosbuvir-ledipasvir only indicated in genotypes 1, 4, 5 and 6.

RESEARCH QUESTION:

Is the treatment with sofosbuvir-velpatasvir safe and effective for the management of chronic hepatitis C virus infection across genotypes.

Eligibility criteria for review

PICO:

Population	Treatment of chronic hepatitis C virus infection (all genotypes)
Intervention	Sofosbuvir-velpatasvir regimen
Comparator/s	Sofosbuvir-velpatasvir regimen plus ribavirin OR Placebo *(Historical comparator/standard of care: pegylated interferon + ribavirin)*
Outcome/s	• Sustained virological response after 12 weeks (SVR12) • Adverse events
Study design/s	Systematic Reviews and Meta-analysis Randomised controlled trials

METHODS

A rapid search of evidence was conducted in PubMed and the Cochrane Library on 1 March 2023. The search strategy is outlined in Appendix 2. A search was initialled conduced for systematic review and meta-analyses and thereafter run for randomised controlled trials to ensure no important areas were excluded, and investigate specific comparisons and genotypes. Data extraction was conducted by JR and reviewed by the ERC. An AMSTAR 2 assessment was conducted independently and in duplicate on the selected systematic review (KM and JR).

RESULTS

Results of the search

The search for systematic and meta-analyses produced 19 results and after title and abstract screening, 4 records remained (2 systematic reviews and meta-analysis). After full text review one study (systematic review and meta-analysis) was included. The search for randomised trials identified 1 study in the HIV and HCV co-infected population that was not included in the identified systematic review record but matched our study PICO. No direct comparison on sofosbuvir/velpatasvir and the historic standard of care pegylated interferon and ribavirin found, thus an additional search was conducted to establish the effect size of pegylated interferon and ribavirin for comparative evaluation. Three phase II randomised controlled trials were included, resulting in a total of 2 systematic reviews and 4 trials included (See Appendix 3 – Characteristics of included studies). A summary of the excluded studies can be found in Appendix 4. Data from studies were extracted and are summarised narratively below (See - Effects of the intervention)

Description of studies included (see appendix 3)

- Ren *et al*. 2022[9] conducted a meta-analysis to investigate the safety and efficacy of sofosbuvir-velpatasvir treatment for chronic hepatitis C virus infection, as well as to understand the effect of this combination with the addition of ribavirin. Inclusion criteria were: hepatitis C virus infected patient (all genotypes) with or without cirrhosis on sofosbuvir-velpatasvir or sofosbuvir-velpatasvir with ribavirin; and evaluating rates of SVR12 and risk of adverse effects. Only randomised trials were included. After a comprehensive literature search (PubMed, Cochrane, EMBASE and Web of Science, five studies where included, n=1277 (See table 1)
  - » Table 1: Key studies included in Ren et al. 2022:

Study	Study type	Population	Genotype	Treatment
Takehara et.al. 2019[10]	Phase 2, open label, randomised trial (n = 102)	HCV and compensated cirrhosis	3	Sofosbuvir/velpatasvir for 12 weeks OR Sofosbuvir/velpatasvir plus ribavirin for 12 weeks
Esteban et.al. 2018[11]	Phase 3, open label, randomised trial (n = 204)	HCV with decompensated cirrhosis	Any	Sofosbuvir/velpatasvir for 12 weeks OR Sofosbuvir/velpatasvir plus ribavirin for 12 weeks
Feld et.al. 2015 (ASTRAL 1)[12]	Phase 3, double-blind, placebo controlled (n = 624)	HCV including those compensated cirrhosis (treated and previously treated)	1 - 6	Sofosbuvir/velpatasvir for 12 weeks OR Matching placebo for 12 weeks

Foster et.al. 2015 (ASTRAL 2,3)[13]	2 x phase 3 RCT open-label studies (genotype 2, n = 266; genotype 3, n = 552)	HCV not treated, including patients with compensated cirrhosis	2, 3	Trial 1 (genotype 2): sofosbuvir/velpatasvir for 12 weeks OR Sofosbuvir/ribavirin for 12 weeks. Trial 2 (genotype 3): sofosbuvir/velpatasvir for 12 weeks OR Sofosbuvir/ribavirin for 24 weeks.
Curry et.al. 2015 (ASTRAL 4)[14]	Phase 3, open-label randomised study (n = 267)	Treated and untreated patients with HCV with decompensated cirrhosis	1-6	Sofosbuvir/velpatasvir for 12 weeks OR Sofosbuvir/velpatasvir plus ribavirin for 12 weeks OR Sofosbuvir/velpatasvir for 24 weeks

Table 2 outlines the details of an additional randomised trials identified in our search that was not included in Ren et al. 2022. ASTRAL 5 (part of the ASTRAL trial series) was not included in Ren et. al, however included the population of adults with HIV and HCV co-infection. This population is applicable to South Africa and thus this study was included.

Table 2: Additional RCT not included in Ren et.al. 2022

Study	Study type	Population	Genotype	Treatment
Wyles et.al.[15] (ASTRAL 5)	Phase 3, open label study.	Adults chronically infected with HIV-1 and HCV	Any genotype	Sofosbuvir/velpatasvir for 12 weeks
Manns et. al. 2001[16]	Randomised controlled phase 3 study	Patients with chronic hepatitis C (n = 1530)	Any	Interferon alfa-2b (3 MU subcutaneously three times per week) plus ribavirin 1000-1200 mg/day orally; Or Peginterferon alfa-2b 1.5 mcg/kg each week plus 800 mg/day ribavirin; Or Peginterferon alfa-2b 1.5 mcg/kg per week for 4 weeks then 0.5 mcg/kg per week plus ribavirin 1000-1200 mg/day for 48 weeks.
Fried MW et.al. 2002[17]	Multinational Randomised controlled trial	Patients with chronic hepatitis C (n = 1121)	Any	Peginterferon alfa-2a 180 mcg once weekly plus daily ribavirin Or Peginterferon alfa-2a weekly plus daily placebo, Or Interferon alfa-2b 3MU thrice weekly plus daily ribavirin for 48 weeks.
Hadzivannis et. al. 2004[18]	Randomised controlled phase 3 study	Patients with chronic hepatitis C (n = 1311)	Any	Peginterferon-α2a, 180 mcg/week, for 24 or 48 weeks plus a low-dose ribavirin.

Effects of Interventions

Efficacy

Sustained virological response of sofosbuvir-velpatasvir for 12-weeks

Ren et al. 2022 reported that sofosbuvir-velpatasvir achieved sustained virological response (SVR12) rates of 94.2% (95% CI 90.7–97.7%, *P* < .001) in 1277 patients[9]. The additional open-label trial (Wyles et al[15]) reported SVR12 results of 95% for the HIV/HCV co-infected population. Table 3 shows results for individual studies within Ren et al. as well as the additional trial included (Wyles et al) Figure 1 shows the forest plot from Ren et al. 2022.

Table 3 - Summary of study findings for SVR12 rates

Included record	Study	SVR12
Ren et al. 2022	Takehara et.al. 2019	92% (n = 47 of 51, 95% CI 81 to 98))
	Esteban et.al. 2018	91% (n = 92 of 101, 95% CI 84 to 96)
	Feld et.al. 2015 (ASTRAL 1)	99% (95% CI, 98 to >99)
	Foster et.al. 2015 (ASTRAL 2,3)	Trial 1 – genotype 2: 99% (95% CI 96 to 100) Trial 2 – genotype 3: 95% (95% CI 92 to 98)
	Curry et.al. 2015 (ASTRAL 4)	83% (95% CI 74 to 90)
Additional open-label trial	Wyles et.al. (ASTRAL 5)	95% (95% CI 89 to 99)

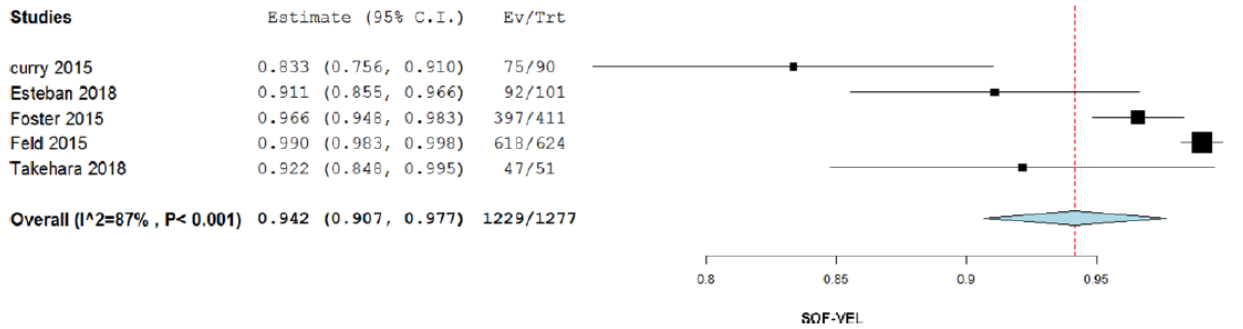

Figure 1 – forest plot from Ren et al. 2022 (Sustained virological response of sofosbuvir-velpatasvir for 12-weeks)[9]

Comparison 1: Sofosbuvir-velpatasvir for 12-weeks vs sofosbuvir/velpatasvir PLUS ribavirin

Ren et al. 2022 reported that 3 RCTS (see Table 4) reported on sofosbuvir-velpatasvir PLUS ribavirin and found that SVR12 rates were similar to sofosbuvir-velpatasvir alone, except in genotype 3.

Table 4: Summary of study findings from Ren et al. 2022

Study	SVR12
Takehara et.al. 2019	92% (n = 47 of 51, 95% CI 81 to 98)
Esteban et.al. 2018	96% (n = 99 of 103, 95% CI 90 to 99)
Curry et.al. 2015 (ASTRAL 4)	94% (95% CI 87 to 98)

The addition of ribavirin to sofosbuvir-velpatasvir did not significantly increase the SVR12 (RR = 1.03, 95%CI [0.95, 1.11]) in HCV genotype-1 patients and the SVR12 (RR = 1.09, 95%CI [0.86, 1.38]) in HCV genotype-2 patients. However, adding ribavirin significantly increased SVR12 (RR = 1.13, 95% CI [1.04, 1.23]) in genotype-3 patients. See Figure 2 below.

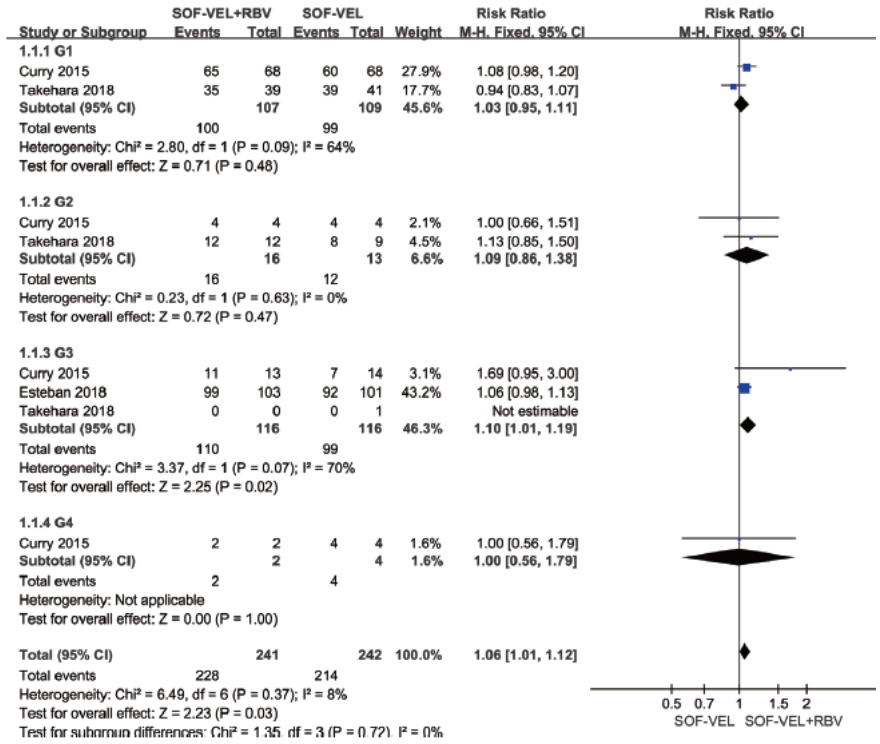

Figure 2 – forest plot from Ren et al. 2022 (Sustained virological response of sofosbuvir-velpatasvir alone compared to sofosbuvir-velpatasvir plus ribavirin or 12-weeks)[9]

Comparison 2: Sofosbuvir-velpatasvir for 12-weeks vs Placebo

Only one study included in Ren et al 2022, evaluated sofosbuvir-velpatasvir versus placebo.[12] Feld et.al. found that sofosbuvir-velpatasvir showed high SVR12 [99% (95% CI 98 to >99)] compared to placebo where no patients had a sustained virological response.

Comparison 3: historical standard of care: Pegylated interferon plus ribavirin

Pegylated interferon plus ribavirin showed a sustained viral response rates of 54% to 63%

Table 5: Sustained virological response from RCTs: *Mann, Fried, Hadziyannis*

Study	Sustained virological response of pegylated interferon plus ribavirin
Manns et. al. 2001	54% (274 of 511 participants)
Fried MW et.al. 2002	56% (254 of 453 participants)
Hadzivannis et. al. 2004	63% (CI 59% to 68%)

Safety

Serious adverse events

No difference in terms of severe adverse events was shown in Ren et al. 2022 between sofosbuvir-velpatasvir group and the sofosbuvir-velpatasvir PLUS ribavirin group (RR = 0.94, 95% CI: 0.55–1.59, P = 0.81, 483 patients).

Safety of sofosbuvir-velapatasvir

Common adverse events reported in Ren et al. 2022 were: anaemia, arthralgia, asthenia, back pain, cough, diarrhea, dyspnea, dyspepsia, fatigue, headache, insomnia, irritability, muscle spasm, myalgia, nasopharyntitis, nausea, prurutis, reduced haemoglobin/anaemia, reduced lymophocytes, and reduced neutrophils. The most frequently occurring events were headache, fatigue, nausea and nasopharyngitis. (See figure 3)

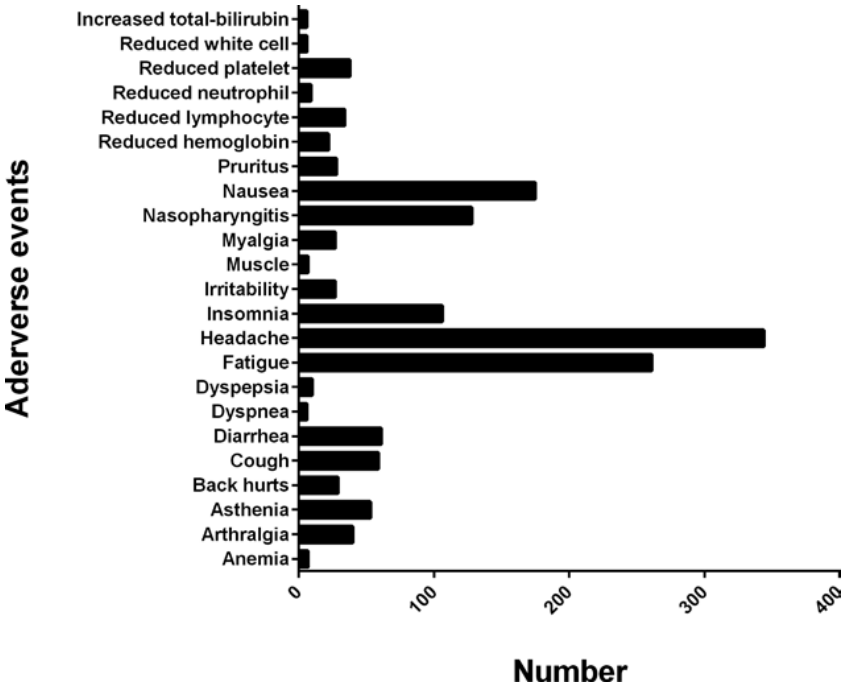

Figure 3: distribution of common adverse events of sofosbuvir-velpatasvir in HCV patients.[9]

Quality of the Evidence

Ren et.al. 2022

Risk of bias was independently assess by two authors. All studies included in the meta-analysis were assessed as low risk of bias in terms of random sequence generation, attrition and reporting biases. All five studies included in the Ren Systematic Review and Meta-analysis were assessed as high risk of bias for performance and detection bias (open-label studies), except Feld et.al. Funnel plot did not reveal significant evidence of publication bias.

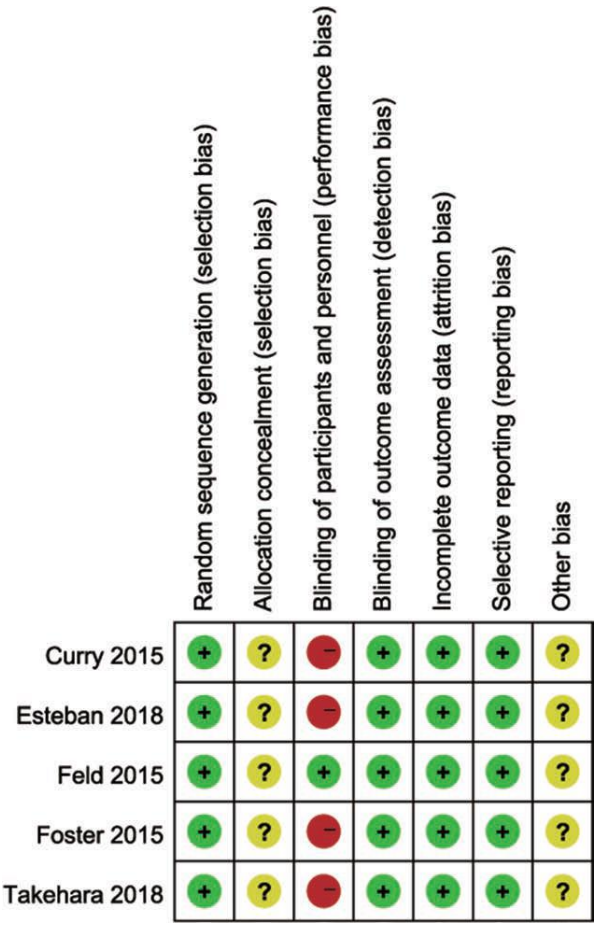

Figure 4: risk of bias summary

AMSTAR:

- Assessed as critically low quality review *(areas contributing to assessment of critically low: no explanation on study selection, included/excluded studies not indicated, no funding sources listed, no explanation son statistical analysis, heterogeneity not clearly discussed, conflicts of interest not listed)*

COSTING AND BUDGET IMPACT

A cost-utility analysis comparing pegylated interferon alfa-2α plus ribavirin with sofosbuvir-velpatasvir with or without ribavirin found sofosbuvir-velpatasvir with or without ribavirin was more cost-effective and cost-saving compared to pegylated interferon alfa-2α plus ribavirin over a 20 year time horizon. The sofosbuvir-velpatasvir with or without ribavirin treatment strategy was dominant, with an ICER of R155 232 and a net monetary benefit of R77 534. A budget impact analysis suggests that full implementation of sofosbuvir-velpatasvir may reduce resource expenditure by 64%, with potential reductions in costs amounting to R63 200 336 over 30 years of management, assuming a 10% annual incremental uptake of sofosbuvir-velpatasvir with or without ribavirin.

See pharmacoeconomic analysis document "Cost-effectiveness of sofosbuvir-velpatasvir for chronic hepatitis C infection: a cost-utility analysis" for details.

CONCLUSION:

Sofosbuvir-velpatasvir has been demonstrated to achieve a sustained virological response rate at 12 weeks (SVR12) of 94%, across genotypes. The addition of ribavirin does not show significant difference in SVR12, except in genotype 3. Adverse effects were shown to be comparable in the groups. The use of sofosbuvir-velpatasvir shows a far better SVR12 as compared to historic standard of care (pegylated interferon and ribavirin) and demonstrated to be cost-effective, even in healthcare settings with limited access to pegylated interferon plus ribavirin. Where genotyping is done, and genotype 3 is present, or in patients with decompensated cirrhosis, consideration can be made for the addition of ribavirin.

Reviewers: Jane Riddin with support of Tertiary Committee, Kim MacQuilkan and Rephaim Mpofu

Declaration of interests:

Jane Riddin (EDP, NDoH) has no interests to declare.

Appendix 1: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High: [ ] Moderate: [X] Low: [ ] Very low: [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Meta-analysis assessed as critically low, and studies included have limitations such as open-label, small sizes. However, there is a high certainty that another study would not materially change the effect size, additionally the findings across studies is shown to be consistent.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large: [X] Moderate: [ ] Small: [ ] None: [ ]	*Large effect size, estimated that 94% sustained virological response at 12 weeks compared to 0% in placebo, and 54-63% in pegylated interferon-ribavirin.*
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High: [ ] Moderate: [X] Low: [ ] Very low: [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large: [ ] Moderate: [ ] Small: [X] None: [ ]	
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention: [X] Favours control: [ ] Intervention = Control *or* Uncertain: [ ]	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes: [X] No: [ ] Uncertain: [ ]	
RESOURCE USE	**How large are the resource requirements?** More intensive: [ ] Less intensive: [X] Uncertain: [ ]	*Considered intervention would likely be cost saving due to improved efficacy and reduced cost.* Cost of medicines/ month: **Medicine** | **Cost (ZAR)*** Sofosbuvir-velpatasvir (Epclusa®) | R6661.54 **state price offer*

VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	The focus of the review was not on this aspect, however the availability of a DAA (sofosbuvir/velpatasvir) allows for treatment options for this group of patients, which stakeholders would value.
EQUITY	**Would there be an impact on health inequity?** Yes [X] No [ ] Uncertain [ ]	Would reduce health inequity. Having access to sofosbuvir/velpatasvir would improve linkage and retention in care and eventually may allow for decentralisation of hepatitis C care from constrained, tertiary level of care to more accessible secondary level of care.

Appendix 2: Search strategy

PUBMED

#	Query	Search Details	Results
5	#1AND #2 AND 3#	**((#1) AND (#2)) AND (#3)** Filters: **Meta-Analysis, Systematic Review**	19
4	#1AND #2 AND 3#	**((#1) AND (#2)) AND (#3)** Filters: **Meta-Analysis, Randomized Controlled Trial, Systematic Review**	38
3		("velpatasvir"[Title/Abstract]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])	43
2	Sofosbuvir	**((sofosbuvir[Title/Abstract]) OR (sofosbuvir[MeSH Terms])** Filters: **Meta-Analysis, Randomized Controlled Trial, Systematic Review**	244
1	Viral hepatitis	**((((hepatitis[MeSH Terms])) OR (viral hepatitis[MeSH Terms])) OR (hepatitis[Title/Abstract])) OR (viral hepatitis[Title/Abstract])** Filters: **Meta-Analysis, Randomized Controlled Trial, Systematic Review**	8672

search	**Query**	**Results**
#1	MeSH descriptor: [Hepatitis, Viral, Human] explode all trees	7138
#2	MeSH descriptor: [Sofosbuvir] explode all trees	313
#3	MeSH descriptor: [velpatasvir] explode all trees	0
#4	#1 AND #2	216
#5	#4 AND velpatasvir	44

RCTS

#	Query	Search Details	Results
4	#1AND #2 AND 3#	**((#1) AND (#2)) AND (#3)** Filters: **Randomized Controlled Trial**	19
3		("velpatasvir"[Title/Abstract] AND ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[All Fields] OR "randomised controlled trial"[All Fields])) AND (randomizedcontrolledtrial[Filter])	23

2	Sofosbuvir	("sofosbuvir"[Title/Abstract] OR "sofosbuvir"[MeSH Terms]) AND (randomizedcontrolledtrial[Filter])	155
1	Viral hepatitis	("hepatitis"[MeSH Terms] OR "hepatitis a"[MeSH Terms] OR (("virally"[All Fields] OR "virals"[All Fields] OR "virology"[MeSH Terms] OR "virology"[All Fields] OR "viral"[All Fields]) AND ("hepatitis"[MeSH Terms] OR "hepatitis a"[MeSH Terms])) OR "hepatitis"[Title/Abstract] OR "viral hepatitis"[Title/Abstract]) AND (randomizedcontrolledtrial[Filter])	5560

COCHRANE LIBRARY

No Cochrane reviews

Additional search for effect size of historic standard of care: pegylated interferon plus ribavirin:

Search: (pegylated interferon plus ribavirin[MeSH Terms]) AND (hepatitis C[MeSH Terms]) Filters: Randomized Controlled Trial Sort by: Publication Date

((("pegylate"[All Fields] OR "pegylated"[All Fields] OR "pegylates"[All Fields] OR "pegylating"[All Fields] OR "pegylation"[All Fields] OR "pegylations"[All Fields]) AND ("interferon s"[All Fields] OR "interferone"[All Fields] OR "interferones"[All Fields] OR "interferons"[Supplementary Concept] OR "interferons"[All Fields] OR "interferon"[All Fields] OR "interferons"[MeSH Terms]) AND "plus"[All Fields]) AND "ribavirin"[MeSH Terms] AND ("hepatitis c"[MeSH Terms] OR "hepacivirus"[MeSH Terms])) AND (randomizedcontrolledtrial[Filter])

- 186 results were identified
- Majority did not meet the PICO: wrong comparator, wrong population, wrong outcome, wrong combination.
- 3 RCTs meeting patient population were included

Appendix 3: Characteristics of included studies

Table 1

Citation	Study design	Population (n)	Treatment	Main findings	Risk of bias
Ren et.al. 2022[9]	Meta-analysis (studies included: • Curry et.al. • Foster et.al. • Feld et.al. • Esteban et.al. • Takehara et.al.	Patients with chronic hepatitis C infection	Sofosbuvir/velpatasvir with or without ribavirin	SVR12 rates of 94.2% (95% CI 90.7 to 97.7%, p <0.001) in patient on sofosbuvir/velpatasvir. Addition of ribavirin did not significantly increase SVR12 in genotypes 1 and 2, RR = 1.03 (95% CI 0.95 to 1.11) and RR = 1.09 (95% 0.86 to 1.38) respectively. Addition of ribavirin in patients with genotype 3 showed significant increased SVR12, RR = 1.13 (95% CI 1.04 to 1.23).	All studies were assessed as low risk of bias in terms of random sequence generation, attrition and reporting biases. All five studies included in the Ren Systematic Review and Meta-analysis were assessed as high risk of bias for performance and detection bias (open-label studies), except Feld et.al. Funnel plot did not reveal significant evidence of publication bias. AMSTAR: assessed as critically low quality

Citation	Study design	Population (n)	Genotypes	Treatment	Main findings	Quality/Risk of bias/limitation
Esteban et.al. 2018	Phase 2, open label, randomised trial	Patients with HCV and compensated cirrhosis (n=204)	3	Sofosbuvir/velpatasvir for 12 weeks OR Sofosbuvir/velpatasvir plus ribavirin for 12 weeks	SVR12 91% (92 of 101, 95% CI 84 to 96) for sof/velpat and 96% (99 of 103, 95% 90 to 99) for sofos/velpat plus rivabvirin group.	» No formal statistical comparison. » Limited patient numbers. » Single country study- may not have external validity.
Takehara et.al. 2019	Phase 3, open label, randomised trial	Patients with HCV with decompensated cirrhosis (n=102)	Any	Sofosbuvir/velpatasvir for 12 weeks OR Sofosbuvir/velpatasvir plus ribavirin for 12 weeks	SVR12 rates were 92% (41 of 51) in each group. Ribavirin did not improve efficacy (but increase toxicity)	» Limited patient numbers » Lack of genotype diversity. » Only few patients with severe cirrhosis included. » Single country study- may not have external validity.

Citation	Study design	Population (n)	Genotypes	Treatment	Main findings	Quality/Risk of bias/limitation
Feld et.al. 2015 (ASTRAL 1)	Phase 3, double-blind, placebo controlled	Patients with chronic HCV genotypes including those with compensated cirrhosis (treated and previously treated) (n=624)	1, 2, 4, 5, 6	Sofosbuvir/velpatasvir OR Matching placebo For 12 weeks	SVR12 was 99% (95% CI, 98 to >99) in patients taking sofosbuvir/velpatasvir. *(none of 116 patients on placebo had a sustained virological response)* *Serious adverse effects in 2% of sofosbuvir/velpatasvir group*	
Foster et.al. 2015 (ASTRAL 2,3)	2 x phase 3 RCT open-label studies	Patients previously treated for HCV genotype 2/3 and those not treated, including patients with compensated cirrhosis (genotype 2, n = 266; genotype 3, n = 552)	2, 3	<u>Trial 1: patients with genotype 2 (n = 266)</u> sofosbuvir/velpatasvir Or Sofosbuvir/ribavirin For 12 weeks. <u>Trial 2: patients with genotype 3 (n = 552)</u> sofosbuvir/velpatasvir for 12 weeks Or Sofosbuvir/ribavirin for 24 weeks.	<u>Trial 1 – genotype 2:</u> SVR12 was 99% (95% CI 96 to 100) in sofosbuvir/velpatasvir group, and 94% (95% CI 88 to 97) in sofosbuvir/ribavirin, p = 0.02. <u>Trial 2 – genotype 3:</u> SVR12 was 95% (95% CI 92 to 98) in sofosbuvir/velpatasvir group, and 80% (95% CI 88 to 97) in sofosbuvir/ribavirin, p < 0.001.	Open-label studies
Curry et.al. 2015 (ASTRAL 4)	Phase 3, open-label randomised study	Treated and untreated patients with HCV genotypes 1-6 with	1-6	Sofosbuvir/velpatasvir for 12 weeks OR	SVR12 sofosbuvir/velpatasvir for 12 weeks: 83% (95% CI 74 to 90) SVR12 sofosbuvir/velpatasvir plus ribavirin for 12 weeks: 94% (95% CI 87 to 98)	Not powered to detect significant differences between 3 groups. Only patients with moderate hepatic decompensation included.

Citation	Study design	Population (n)	Genotypes	Treatment	Main findings	Quality/Risk of bias/limitation
		decompensated cirrhosis (n = 267)		Sofosbuvir/velpatasvir plus ribavirin for 12 weeks OR Sofosbuvir/velpatasvir for 24 weeks	SVR12 sofosbuvir/velpatasvir for 24 weeks: 86% (95% CI 77 to 92) *No significant differences between groups on post hoc analysis*	
Wyles D et.al. (ASTRAL 5)	Phase 3, open-label, single arm study	Patients with HCV (any genotype) and HIV-1 coinfection, including those with compensated cirrhosis (n = 106)	1 - 4	Sofosbuvir/velpatasvir daily for 12 weeks	• SVR12 achieved in 95% of patients (101 of 106), 95% CI, 89%–99% • Genotype 1: SVR12 achieved in 95% patients (74 of 78), 95% CI, 87%–99% • Genotype 2: SVR12 achieved in 100% (all 11) 95% CI, 72%–100% • Genotype 3: SVR12 achieved in 92% (11 of 12) 95% CI, 62%–100% • Genotype 4: SVR12 achieved in 100% (all 5) 95% CI, 48%–100% • All 19 patients with cirrhosis had SVR12.\The most common adverse events were fatigue (25%), headache (13%), upper respiratory tract infection (8%), and arthralgia (8%)	• Numbers of hard to treat patients (i.e. cirrhosis etc.) was small and insufficient to confirm efficacy/safety in co-infected (HIV/HCV) patients – however not expected that HIV-1 adversely impacts response of Sofosbuvir/velpatasvir. • Generalisability limited due to small sample size. • No patients with genotypes 5 and 6 included.

Citation	Study design	Population (n)	Genotypes	Treatment	Main findings	Quality/Risk of bias/limitation
Manns et. al. 2001	Randomised controlled phase 3 study	Patients with chronic hepatitis C (n = 1530)	Any	Interferon alfa-2b (3 MU subcutaneously three times per week) plus ribavirin 1000-1200 mg/day orally; Or Peginterferon alfa-2b 1.5 mcg/kg each week plus 800 mg/day ribavirin; Or Peginterferon alfa-2b 1.5 mcg/kg per week for 4 weeks then 0.5 mcg/kg per week plus ribavirin 1000-1200 mg/day for 48 weeks.	SVR rate was significantly higher in the higher-dose peginterferon group (274/511 [54%],)) than in the lower-dose peginterferon (244/514 [47%]) or interferon (235/505 [47%]) groups. p = 0.01 for both comparisons.	•
Fried MW et.al. 2002	Multinational Randomised controlled trial	Patients with chronic hepatitis C (n = 1121)	Any	Peginterferon alfa-2a 180 mcg once weekly plus daily ribavirin Or Peginterferon alfa-2a weekly plus daily placebo, Or Interferon alfa-2b 3MU thrice weekly plus daily ribavirin for 48 weeks.	A higher proportion of patients who received peginterferon alfa-2a plus ribavirin had a sustained virologic response (defined as the absence of detectable HCV RNA 24 weeks after cessation of therapy) than of patients who received interferon alfa-2b plus ribavirin (56 percent vs. 44 percent, $p < 0.001$) or peginterferon alfa-2a alone (56 percent vs. 29 percent, $p < 0.001$).	• Study was designed by sponsor together with hepatologists • Data analysis included sponsors
Hadzivannis et. al. 2004	Randomised controlled phase 3 study	Patients with chronic hepatitis C (n = 1311)	Any	Peginterferon-α2a, 180 mcg/week, for 24 or 48 weeks plus a low-dose ribavirin.	Sustained virologic response rates for peginterferon-α2a and standard-dose ribavirin for 48 weeks were 63% (CI, 59% to 68%) overall and 52% (CI, 46% to 58%) in patients with HCV genotype 1	•

Appendix 4: Excluded studies

Citation	Article Type	Reason for exclusion
Safety and efficacy of **sofosbuvir** plus **velpatasvir** with or without ribavirin for chronic **hepatitis** C virus infection: A systematic review and meta-analysis. Ahmed H, Abushouk AI, Attia A, Gadelkarim M, Gabr M, Negida A, Abdel-Daim MM.J Infect Public Health. 2018 Mar-Apr;11(2):156-164. doi: 10.1016/j.jiph.2017.09.004. Epub 2017 Sep 29.PMID: 28970099	Systematic review and meta-analysis	A later updated SR and MA included
Effectiveness and Safety of **Sofosbuvir**/**Velpatasvir**/Voxilaprevir as a **Hepatitis** C Virus Infection Salvage Therapy in the Real World: A Systematic Review and Meta-analysis. Xie J, Xu B, Wei L, Huang C, Liu W.Infect Dis Ther. 2022 Aug;11(4):1661-1682. doi: 10.1007/s40121-022-00666-0. Epub 2022 Jun 24.PMID: 35749010	Systematic review and meta-analysis	Does not meet PICO
Safety of interferon-free therapies for chronic **hepatitis** C: a network meta-analysis. Ferreira VL, Assis Jarek NA, Tonin FS, Borba HH, Wiens A, Pontarolo R.J Clin Pharm Ther. 2016 Oct;41(5):478-85. doi: 10.1111/jcpt.12426. Epub 2016 Jul 21.PMID: 27440554	Network meta-analysis	Does not meet PICO
Sofosbuvir plus **velpatasvir** combination for the treatment of chronic **hepatitis** C in patients with end stage renal disease on renal replacement therapy: A systematic review and meta-analysis. De A, Roy A, Verma N, Mishra S, Premkumar M, Taneja S, Singh V, Duseja A.Nephrology (Carlton). 2022 Jan;27(1):82-89. doi: 10.1111/nep.13968. Epub 2021 Sep 14.PMID: 34453374	Systematic review and meta-analysis	Does not meet PICO
Identification of the Best Direct-Acting Antiviral Regimen for Patients With **Hepatitis** C Virus Genotype 3 Infection: A Systematic Review and Network Meta-analysis. Berden FA, Aaldering BR, Groenewoud H, IntHout J, Kievit W, Drenth JP.Clin Gastroenterol Hepatol. 2017 Mar;15(3):349-359. doi: 10.1016/j.cgh.2016.10.034. Epub 2016 Nov 10.PMID: 27840182	Systematic review and network meta-analysis	Does not meet PICO
Interferon-free therapies for patients with chronic **hepatitis** C genotype 3 infection: A systematic review. Gimeno-Ballester V, Buti M, San Miguel R, Riveiro M, Esteban R.J Viral Hepat. 2017 Nov;24(11):904-916. doi: 10.1111/jvh.12660. Epub 2017 Jan 23.PMID: 27925386	Systematic review	Does not meet PICO
Transplant of Kidneys From **Hepatitis** C Virus-Positive Donors To **Hepatitis** C Virus-Negative Recipients: A Retrospective Study and Systematic Review. Shadekejiang H, Zhu J, Wu X.Exp Clin Transplant. 2022 Dec;20(12):1076-1084. doi: 10.6002/ect.2022.0315.PMID: 36718006	Retrospective study and systematic review	Does not meet PICO/and study design
Effectiveness of current and future regimens for treating genotype 3 **hepatitis** C virus infection: a large-scale systematic review. Fathi H, Clark A, Hill NR, Dusheiko G.BMC Infect Dis. 2017 Nov 16;17(1):722. doi: 10.1186/s12879-017-2820-z.PMID: 29145802	Systematic review	Does not meet PICO
Systematic review: current concepts and challenges for the direct-acting antiviral era in **hepatitis** C cirrhosis. Majumdar A, Kitson MT, Roberts SK.Aliment Pharmacol Ther. 2016 Jun;43(12):1276-92. doi: 10.1111/apt.13633. Epub 2016 Apr 18.PMID: 27087015	Systematic Review	Does not meet PICO

Efficacy and safety of **sofosbuvir**-containing regimens in chronic **hepatitis** C patients with genotype 2 and 3: a comprehensive analysis of 18 randomized controlled trials. Fan H, Huang P, Tian T, Wu J, Xia X, Feng Y, Wang J, Yu R, Zhang Y, Yue M.J Gastrointestin Liver Dis. 2018 Jun;27(2):159-168. doi: 10.15403/jgld.2014.1121.272.sof.PMID: 29922761	Systematic Review	Does not meet PICO
Cost-Effectiveness of Elbasvir/Grazoprevir for the Treatment of Chronic **Hepatitis** C: A Systematic Review. Liu J, Guo M, Ke L, You R.Front Public Health. 2022 May 13;10:836986. doi: 10.3389/fpubh.2022.836986. eCollection 2022.PMID: 35646774	Systematic review	Does not meet PICO
Real-World Effectiveness of Direct-Acting Antiviral Regimens against **Hepatitis** C Virus (HCV) Genotype 3 Infection: A Systematic Review and Meta-Analysis. Zhuang L, Li J, Zhang Y, Ji S, Li Y, Zhao Y, Li B, Li W, Quan M, Duan Y, Zhao H, Cheng D, Wang X, Ou W, Xing H.Ann Hepatol. 2021 Jul-Aug;23:100268. doi: 10.1016/j.aohep.2020.09.012. Epub 2020 Oct 12.PMID: 33059055	Systematic review and meta-analysis	Does not meet PICO
Efficacy and Safety of **Sofosbuvir**-based Regimens in **Hepatitis** C Patients With Decompensated Cirrhosis: A Systematic Review and Meta-analysis. Zhang W, Zhang J, Tang S, Liu Y, Du X, Qiu L, Liu M, Yu H, Pan CQ.J Clin Transl Hepatol. 2023 Feb 28;11(1):144-155. doi: 10.14218/JCTH.2022.00006. Epub 2022 Jun 28.PMID: 36406321	Systematic review and meta-analysis	Does not meet PICO
French Patients with **Hepatitis** C Treated with Direct-Acting Antiviral Combinations: The Effect on Patient-Reported Outcomes. Cacoub P, Bourliere M, Asselah T, De Ledinghen V, Mathurin P, Hézode C, Henry L, Stepanova M, Younossi ZM.Value Health. 2018 Oct;21(10):1218-1225. doi: 10.1016/j.jval.2018.01.006. Epub 2018 Feb 21.PMID: 30314623	Systematic Review	Does not meet PICO
Systematic review: epidemiology and response to direct-acting antiviral therapy in genotype 6 chronic **hepatitis** C virus infection. Mettikanont P, Bunchorntavakul C, Reddy KR.Aliment Pharmacol Ther. 2019 Mar;49(5):492-505. doi: 10.1111/apt.15100. Epub 2019 Jan 27.PMID: 30687952	Systematic review	Does not meet PICO
The impact of **sofosbuvir**/**velpatasvir**/voxilaprevir treatment on serum hyperglycemia in **hepatitis** C virus infections: a systematic review and meta-analysis. Hung HY, Lai HH, Lin HC, Chen CY.Ann Med. 2023 Dec;55(1):463-479. doi: 10.1080/07853890.2023.2168745.PMID: 36655629	Systematic review and meta-analysis	Does not meet PICO
Comparative effectiveness of pan-genotypic therapies for the treatment of patients with **hepatitis** C virus infection in Bulgaria. Djambazov S, Slavchev G, Encheva M, Mitova R, Vekov T.J Comp Eff Res. 2019 May;8(7):455-459. doi: 10.2217/cer-2018-0143. Epub 2019 Mar 28.PMID: 30920311		Does not meet PICO
Drug-Drug Interactions between Direct Oral Anticoagulants and **Hepatitis** C Direct-Acting Antiviral Agents: Looking for Evidence Through a Systematic Review. Bellesini M, Bianchin M, Corradi C, Donadini MP, Raschi E, Squizzato A.Clin Drug Investig. 2020 Nov;40(11):1001-1008. doi: 10.1007/s40261-020-00962-y.PMID: 32809123	Systematic review	Does not meet PICO

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