National Essential Medicine List

Tertiary Medication Review Process

Cost-effectiveness of sofosbuvir/velpatasvir for chronic hepatitis C infection: A cost-utility analysis

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EXECUTIVE SUMMARY

Medicine: Sofosbuvir-Velpatasvir (SOF/VEL)
Indication: Chronic viral hepatitis C (B18.2)
Patient population: Patients with chronic hepatitis C infection, with or without cirrhosis
Level of Care: Tertiary and Quaternary Hospital Level
Prescriber level: Specialist (Hepatology/Gastroenterology)

Current Standard of Care/ Comparator(s): Pegylated interferon alfa-2α + Ribavirin (PEG-IFN-2α+RBV). Availability of SOF/VEL is currently limited through treatment access programs.

Methods: A cost-utility analysis was conducted using a decision tree-Markov hybrid model from a public health sector perspective over a 20-year time horizon. Incremental cost-effectiveness ratios and net monetary benefit were used to assess cost-effectiveness with willingness-to-pay thresholds of R 40 000/QALY and R0/QALY. Price affordability and budget impact analyses were also conducted.

Findings: SOF/VEL±RBV was more effective and cost-saving compared to PEG-IFN-2α+RBV. Per patient treatment costs were decreased by R77 534, while per patient QALYs increased by 0.50 QALYs over 20 years. The SOF/VEL±RBV treatment strategy was dominant, with an ICER of -R155 232 and a net monetary benefit of R77 534. SOF/VEL±RBV also reduced the incidence of liver disease-related mortality, decompensated cirrhosis, hepatocellular carcinoma, and liver transplantation. Price affordability analyses suggested that SOF/VEL may cease to be cost-effective at an estimated monthly price of R41 064 (95% CI: R39 879 to R42 308) per month with a WTP of R40 000, while SOF/VEL would cease to be cost-effective at an estimated monthly price of R 34 371 (95% CI R33 346 to R35 448) with a cost-neutral approach. A budget impact analysis suggests that full implementation of SOF/VEL 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 SOF/VEL±RBV.

Recommendations: 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 infection.

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Conflicts of interest: None to declare.

INTRODUCTION

In South Africa, the estimated prevalence of hepatitis C infection is between 0.4% and 1.7% of the population, indicating that around 600 000 individuals require treatment at any given moment.[1, 2] If left untreated, hepatitis C infection can lead to chronic hepatitis, cirrhosis, and hepatocellular carcinoma, which are associated with significant morbidity and mortality and major resource requirements to treat.[3] Traditionally, antiviral drugs such as ribavirin and pegylated interferon alfa-2α (PEG-IFN-2α) have been used to treat hepatitis C in South Africa, with sustained virological response (SVR) rates of 30-75%.[3] However, since 2014, direct-acting antiviral agents (DAAs) such as sofosbuvir and velpatasvir have become more widely used internationally due to their high efficacy and lower toxicity compared to traditional therapies.[3] These drugs work by preventing RNA replication through the inhibition of non-structural 5B (NS5B) and non-structural 5A (NS5A) proteins respectively.[4] The sofosbuvir and velpatasvir combination has been added to the World Health Organization's (WHO) Model List of Essential Medicines, indicating their importance in the management of people with chronic hepatitis C infection.[5]

Despite these benefits, cost remains a significant barrier to access for these agents, especially among many low- and middle-income countries including South Africa. Previous pharmacoeconomic analyses have found that treatment with SOF/VEL can be cost-effective, but pricing remains an important barrier to access in many countries.[6-8] The originator pharmaceutical company entered into voluntary license agreements with 101 emerging market countries. These agreements allow for the production and sale of generic versions of these drugs. As a result, South Africa is able to access these medications at a reduced cost for a complete course of treatment.[9] This important class of drugs may be cost-effective and affordable at these prices.

A motivation was received for SOF/VEL to be added to the South African Essential Medicines List for the treatment of chronic hepatitis C infection, and the efficacy and safety has previously been reviewed. This report presents the findings of a cost-utility analysis for SOF/VEL in patients with hepatitis C in South Africa.

METHODOLOGY

A cost-utility approach was used for this pharmacoeconomic analysis. Two treatment regimens were assessed:

1. Pegylated interferon alfa-2α and ribavirin (PEG-IFN-2α+RBV) – PEG-IF-2α 180 mcg once weekly subcutaneously and weight-based ribavirin daily for 48 weeks. Patients with decompensated cirrhosis that were assigned to this treatment cohort did not receive any antiviral therapy (see details below).
2. Sofosbuvir-velpatasvir with or without ribavirin (SOF/VEL±RBV) – SOF/VEL 400/100 mg daily, orally for 12 weeks. Weight-based ribavirin was added for patients with compensated or decompensated cirrhosis for 12 weeks.

Ribavirin dose was adjusted based on total body weight, with patients weighing less than 75kg receiving 1 000 mg daily and those weighing 75 kg or more receiving 1 200 mg. Patients with acute hepatitis C infection were not included in this analysis. A hypothetical population of patients with chronic hepatitis C was simulated based on the current epidemiology in South Africa. A decision tree-Markov hybrid model was developed to simulate the disease progression of chronic hepatitis C infection after treatment with PEG-IFN-2α+RBV or SOF/VEL±RBV. Similar model frameworks have been used previously to assess the cost-effectiveness of DAAs.[7, 10-12] The analysis begins with a decision tree which results in two health state outcomes (SVR or failed SVR), based on the probability

of SVR for each treatment regimen. Patients entered the decision tree with a baseline health state of chronic hepatitis without cirrhosis (68%), compensated cirrhosis (20%), or decompensated cirrhosis (12%) based on the reported epidemiology of chronic hepatitis C infection.[13, 14] Following treatment, patients could remain in their health state or transition into one of the following health states once per cycle: chronic hepatitis, compensated cirrhosis, decompensated cirrhosis, liver transplantation, hepatocellular carcinoma, post-liver transplantation, post-treatment of hepatocellular carcinoma, or death (either related to liver disease or unrelated) depending on derived transition probabilities from available literature.[15-31] The probability of non-liver related death was modelled based on an age-adjusted probability of death due to natural causes. Patients with chronic hepatitis without cirrhosis that achieved SVR were assumed to have been cured completely and were thus no longer at risk of clinical progression of liver disease. By contrast, patients with chronic hepatitis without cirrhosis that failed to achieve SVR, and those with cirrhosis (including patients that achieved SVR and those failing to achieve SVR), were modelled to have varying risks of clinical progression of liver disease after antiviral therapy. Those that failed to achieve SVR did not receive repeat antiviral therapy/re-treatment. The full model is shown in Figure 1. The Markov model used a 1-year cycle length and 20-year time horizon, with half-cycle correction using the trapezoidal method.[32]

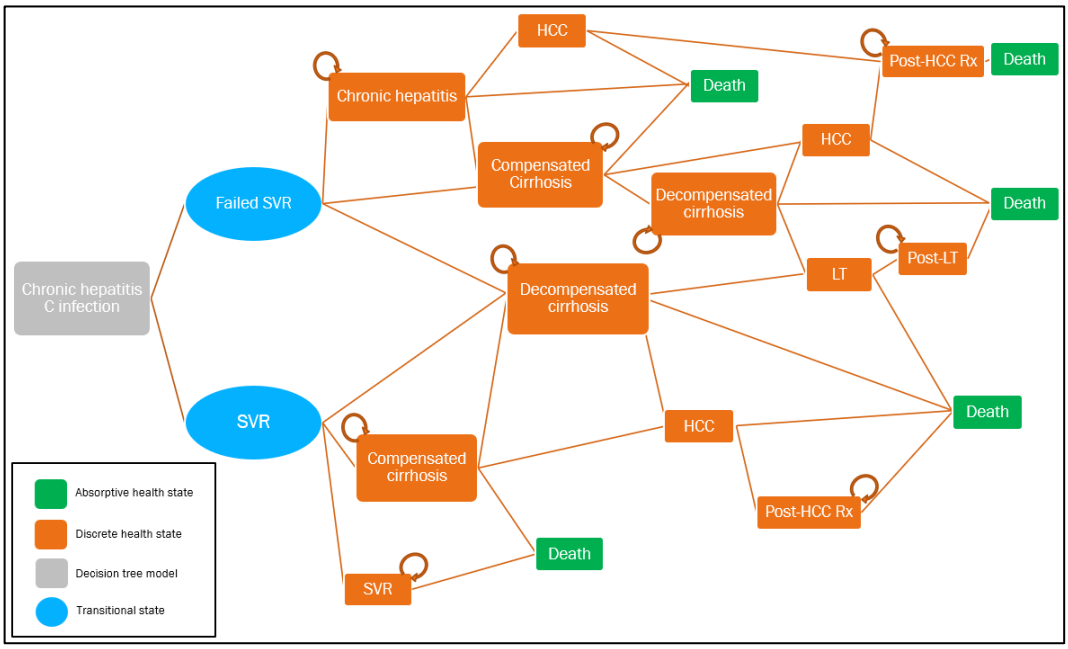

Figure 1. Model structure of the decision tree-Markov simulation. Patients can either transition from one health state to another (left-to-right sequence) once per cycle or remain in the same health state for that cycle. HCC = Hepatocellular carcinoma, LT = Liver transplantation, Post-HCC Rx =Post-treatment of hepatocellular carcinoma, Post-LT = Post Liver transplantation, SVR = Sustained virological response.

Costing inputs

The analysis was conducted from a healthcare payer perspective and only included direct medical costs. Costs were based on 2022 South African currency (R), and historical costs were adjusted for inflation where required.[33] Expenses considered for each treatment regimen were drug costs (Table 1), specialist consultation costs, adverse event costs, monitoring costs at the start of treatment and throughout the course of management, costs for the management of HCC, costs of liver transplantation, and costs related to the management of decompensated cirrhosis including hospitalisation. Drug costs were based on 2022 South African tender prices.[34] Costs were adjusted

for discounting and inflation using a discounting rate of 5% and an inflation rate of 5.3% (10-year geometric mean from 2009-2019).[35, 36] Other costs are listed in Appendix 1.

Table 1. Pharmaceutical drug costs

Active ingredient	Units per pack	Pack cost	Treatment cost per week (<75 kg)	Treatment cost per week (≥75 kg)
PEG-interferon alfa-2α 180 mcg injectable	1	R1 361.20	R1 361.20	R1 361.20
Ribavirin 200 mg tablets	42	R315.50	R262.92	R315.50
Sofosbuvir/velpatasvir 500 mg tablets	28	R6 661.00	R1 665.25	R1 665.25

Clinical inputs

Data for treatment efficacy estimates for SOF/VEL±RBV and PEG-IFN-2α+RBV regimens were extracted from randomised clinical trials and, where necessary, observational studies.[15-31] These data were stratified by stage of disease progression into chronic hepatitis, compensated cirrhosis, and decompensated cirrhosis, and meta-analysed to form efficacy parameters for the base-case and probabilistic models (Table 2). As interferon-based therapy is traditionally contraindicated in patients with decompensated cirrhosis[37], patients assigned to the PEG-IFN-2α+RBV cohort with decompensated cirrhosis did not receive antiviral therapy, but were instead managed as their liver disease progressed or hepatocellular carcinoma developed. The incidence and management of clinically relevant, treatment-emergent adverse events (dermatitis/rash, depression, and anaemia) were included in the model, based on a previous health technology assessment conducted by Canadian Agency for Drugs and Technologies in Health for SOF/VEL.[38] Other input parameters are available in Appendix 1.

Table 2. Efficacy estimates of treatment regimens by health state

Health State	PEG-IFN-2α+RBV (95% CI)	SOF/VEL±RBV (95% CI)
Chronic hepatitis	65% (63%, 68%)	98% (97%, 99%)
Compensated cirrhosis	47% (44%, 51%)	96% (93%, 98%)
Decompensated cirrhosis	No Hepatitis C treatment received	83% (74%, 90%)

Outcomes

An incremental cost-effectiveness ratio (ICER) was calculated to estimate the cost-effectiveness of the SOF/VEL±RBV treatment regimen based on a willingness to pay threshold of R 40 000/QALY derived from Edoka et al.[39] The incremental net monetary benefit (NMB) was also calculated by multiplying the incremental QALYs between the two treatment regimens by the willingness to pay (WTP) threshold, followed by subtracting it from the incremental costs. The SOF/VEL treatment regimen was considered cost-effective if the NMB was greater than zero. Predicted health outcomes 20 years after treatment, namely SVR, mortality (liver-related and non-liver related), hepatocellular carcinoma, and liver transplantation requirements were also assessed. To evaluate the burden of disease in each health state, the total duration of patient follow-up and management was quantified in person-years.

Input parameter distributions

Input parameters were modelled using known or previously reported distributions including normal, beta, and binomial distributions.[7] Parameter distributions that were not readily available from literature or had a high level of uncertainty were modelled using triangular distributions with estimated mean, and plausible minimum and maximum values (Appendix 1).

Price threshold analysis

A price threshold analysis was conducted to determine the price of SOF/VEL at which it would cease to be cost-effective. To calculate the ICERs, we used the probabilistic model and performed 1 000 iterations of a two-level Monte Carlo simulation, considering various price points relative to the current cost of sofosbuvir-velpatasvir. We initiated the simulation with an 80% discount from the base-case drug cost of SOF/VEL and incrementally increased the drug cost at regular intervals (e.g., -60%, -40%, -20%, 10%, 20%, 40%, 50%, etc.) to determine the ICER at each price point. To establish the point at which SOF/VEL±RBV would cease to be cost-effective, we assessed the linear relationship between the cost of SOF/VEL and the ICER by determining the slope and intercept from simulated ICERs at incremental SOF/VEL costs, and determined the intersection point between this linear relationship and that of an ICER with the value of the WTP. We assessed various WTP thresholds to determine the maximum SOF/VEL cost that would remain cost-effective, if at all: R0/QALY to assess a scenario of cost-neutrality, R40 000/QALY, and R101 803/QALY based on the 2022 gross domestic profit per capita (1xGDP). Ninety-five percent confidence intervals (95% CI) were estimated using a bootstrap method to quantify uncertainty.

Budget impact analysis

A budget impact analysis was conducted by modelling the relative cost of incremental uptake of SOF/VEL±RBV at 10% per annum, starting at 10% uptake in the first year. Total management costs were assessed and compared with a scenario where eligible patients are only treated with PEG-IFN-2α+RBV. The population of patients with chronic hepatitis C requiring treatment was modelled to increase by 1.3% per year[40], and costs were also subject to discounting and inflation adjustments as previously described.

Sensitivity analyses

Univariable (one-way) and probabilistic sensitivity analyses were conducted to assess uncertainty in the model. Model input parameters were entered stochastically to assess their impact on the ICER using values on the 25th and 75th centiles, sampled from their modelled distributions. Percent changes in ICER were displayed in a tornado diagram. For the probabilistic sensitivity analysis, a Monte Carlo simulation was performed with 1 000 simulations, and the results were graphed on a cost-effectiveness plane. The probability of acceptability across a range of WTP thresholds, up to R120 000 per QALY, were graphed on a cost-effectiveness acceptability curve (CEAC). Due to potential differences in treatment efficacy estimates by viral genotype (primarily due to varying efficacy with PEG-IFN-2α+RBV therapy), we performed a sensitivity to assess the cost-effectiveness by the following genotype groups: a) genotype 1, b) genotypes 2-3, and c) genotypes 4, 5, and 6. In addition, the base-case model assumed that all patients eligible to receive PEG-IFN-2α+RBV have access to it, however, disparities in healthcare access may have a significant impact on the generalisability of these results. To evaluate the potential impact of this assumption, we conducted a sensitivity analysis by assessing the cost-effectiveness of the SOF/VEL±RBV regimen using varying proportions of patients eligible for treatment with interferon-based therapy, who are actually treated. The tested range for the proportion of treated patients spanned from 0% to 100%.

This analysis was performed using Microsoft Excel 365 and Microsoft Azure cloud computing services.[41, 42]

RESULTS

Base Case analysis

Two hypothetical cohorts with chronic hepatitis C were assessed using the investigational treatment strategies (size of each cohort = 139). Mean initial treatment costs amounted to R90 243 and R32 829 per patient in the PEG-IFN-2α+RBV and SOF/VEL±RBV groups respectively, resulting in decreased treatment costs of R57 414 (Table 3). Initial treatment costs were also decreased in the SOF/VEL±RBV group whether patients had chronic hepatitis or compensated cirrhosis at the time of treatment (Appendix 2). Pharmaceutical drug costs accounted for the majority of resource expenditure in both treatment groups during the initial treatment period (R64 334 per patient for PEG-IFN-2α+RBV and R21 134 per patient for SOF/VEL±RBV; Table 3). Management costs of treatment-emergent adverse events were significantly reduced in those treated with SOF/VEL±RBV (R12 493 per patient) compared to those managed with PEG-IFN-2α+RBV (R3 079 per patient; Table 3).

Long-term management costs over the 20-year time span were decreased in the cohort treated with SOF/VEL±RBV compared to those treated with PEG-IFN-2α+RBV, with mean management costs of R29 447 and R49 567 per patient respectively (Table 4). When stratified by health state (Table 5), management costs for patients with chronic hepatitis without cirrhosis in the PEG-IFN-2α+RBV cohort were significantly higher, largely due to the inferior SVR rate of this regimen resulting in patients experiencing a greater number of patient-years in health states that required monitoring for the clinical progression of liver disease. Management costs for those with compensated cirrhosis were marginally greater among those treated with SOF/VEL±RBV compared to those that received PEG-IFN-2α+RBV, largely due to the increased efficacy of DAAs which resulted in more stable liver function and slower progression of liver cirrhosis over the observed period (Table 5). This resulted in a relative increase in monitoring costs in the SOF/VEL±RBV group. Management costs of those with decompensated cirrhosis were marginally increased in the cohort of patients treated with PEG-IFN-2α+RBV compared to those treated with SOF/VEL±RBV, with the less than expected difference largely due to an increased duration of survival and reduced mortality among those treated with SOF/VEL±RBV compared to those treated with PEG-IFN-2α+RBV (Table 5). In this subgroup of patients, while monitoring and imaging costs, as well as costs associated with the management of decompensated cirrhosis, were higher in the group treated with SOF/VEL±RBV, this increase was offset by a 7-fold increase in costs due to liver transplantation in the PEG-IFN-2α+RBV group. Management costs of patients in the PEG-IFN-2α+RBV group were also considerably greater due to higher incidence of hepatocellular carcinoma in this group (Table 5).

Table 3. Initial treatment costs per-patient by intervention and cost category

Management modalities	PEG-IFN-2α+RBV (%total costs)	SOF/VEL±RBV (%total costs)
Drug costs (total)	R64 334 (71%)	R21 134 (64%)
Human resource costs	R2 590 (3%)	R706 (2%)
Lab test costs	R9 312 (10%)	R6 395 (19%)
Liver U/S elastography and biopsy‡	R1 515 (2%)	R1 515 (5%)
Adverse event costs†	R12 493 (14%)	R3 079 (9%)
Total costs	**R90 243**	**R32 829**

†Adverse events included dermatitis/rash, depression, and anaemia based on a previously conducted health technology assessment by the Canadian Agency for Drugs and Technologies in Health.[41]

‡As liver ultrasound (U/S) elastography and liver biopsies are not routinely performed, these procedures were limited to a small proportion of patients where the procedure may have potentially been indicated (10% for liver U/S elastography and 5% for liver biopsies).

Table 4. Base case analysis for the cost-effectiveness of sofosbuvir-velpatasvir

	Management costs					
Treatment interventions	**Initial**	**Long-term**	**Total**	**QALYs**	**ICER**	**NMB**
PEG-IFN-2α+RBV	R90 243	R49 567	R139 810	4.59		
SOF/VEL± RBV	R32 829	R29 447	R62 275	5.09		
Incremental			-R77 534	0.50	-R155 232	
NMB (WTP = R40 000)						R97 513
NMB (WTP = R0)						R77 534

Note: ICER = Incremental cost-effectiveness ratio, NMB = Net monetary benefit. Net monetary benefit is calculated by calculating the difference between benefit gained (QALYs quantified in monetary terms by multiplying by the willingness to pay [WTP] threshold) and costs required to obtain the benefit. An NMB greater than zero indicates that the SOF/VEL± RBV treatment strategy would be cost-effective.

Treatment with SOF/VEL±RBV improved health outcomes over time compared with the PEG-IFN-2α+RBV regimen, with a higher incidence of SVR (n = 75/139 [54%] for PEG-IFN-2α+RBV vs 133/139 [96%] for SOF/VEL±RBV; Table 6 and Figure 2), decreased incidence of decompensated cirrhosis (19/139 [14%] patients vs 3/139 [2%] patients), decreased incidence of hepatocellular carcinoma (6/139 [4%] patients vs 0.5/139 [0.3%] patient), decreased requirement for liver transplantation procedures (0.1/139 [0.1%] patients vs 0.02/139 [0.01%] patients), and decreased liver disease-related mortality (19/139 [14%] vs 10/139 [7.3%]) over the 20-year period.

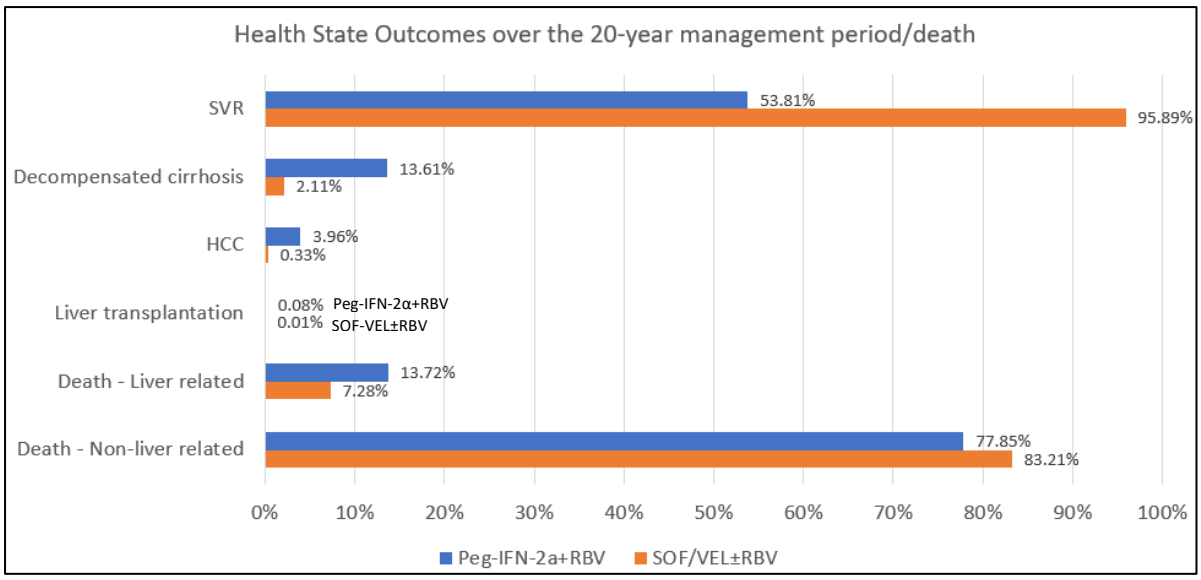

Figure 2. Health state outcomes over the 20 year management period. Participants treated with antiviral therapy (except those in decompensated cirrhosis assigned to the PEG-IFN-2α cohort) were managed over 20 years, or until death occurred. Proportions indicate the number of participants with that outcome out of the total number of patients in the treatment cohort (n = 139). Participants may have experienced more than one health state over the management period, e.g., decompensated cirrhosis leading to liver transplantation and ending in liver related death. HCC = Hepatocellular carcinoma, Peg-IFN-2α+RBV = Pegylated interferon-2α and ribavirin, SOF/VEL±RBV = Sofosbuvir/Velpatasvir with or without ribavirin, SVR = Sustained virological response.

Patients treated with SOF/VEL±RBV gained an additional 0.50 QALYs compared to those treated with the standard of care (4.59 QALYs per patient vs 5.09 QALYs per patient in the PEG-IFN-2α+RBV and SOF/VEL±RBV groups respectively; Table 4). Stratified by health state throughout the management period, patients that had chronic hepatitis without cirrhosis and were treated with SOF/VEL±RBV and subsequently had a SVR, gained the greatest number of QALYs compared to those treated with PEG-IFN-2α+RBV (Figure 3). A significant number of QALYs were also gained by patients with decompensated cirrhosis in the cohort that were treated with SOF/VEL±RBV compared to those assigned to the PEG-IFN-2α+RBV regimen cohort. This difference was primarily because patients assigned to PEG-IFN-2α+RBV did not receive antiviral therapy, as interferon-based regimens are generally not recommended for individuals with advanced liver disease. However, literature indicates that treatment with SOF/VEL±RBV would still likely result in a net increase in QALYs, as clinical trials have shown SVR rates of 83% (95% CI 74%, 90%) for those treated with SOF/VEL±RBV, while a meta-analysis of trials involving decompensated cirrhosis patients treated with interferon and ribavirin suggests a potential SVR rate of 24% (95% CI 19%, 30%).[19, 29-31]

From this base-case analysis of incremental costs and benefits, the interventional treatment strategy with SOF/VEL±RBV dominated the PEG-IFN-2α+RBV strategy with an ICER of R-155 232 (Table 4). The calculated NMB was R97 513 with a WTP threshold of R40 000, indicating that treatment with the SOF/VEL±RBV regimen was cost-effective and cost-saving (Table 4). Using a cost-neutrality approach with a WTP threshold of R0, SOF/VEL±RBV was still cost-effective and cost saving, with an NMB of R77 534 (Table 4).

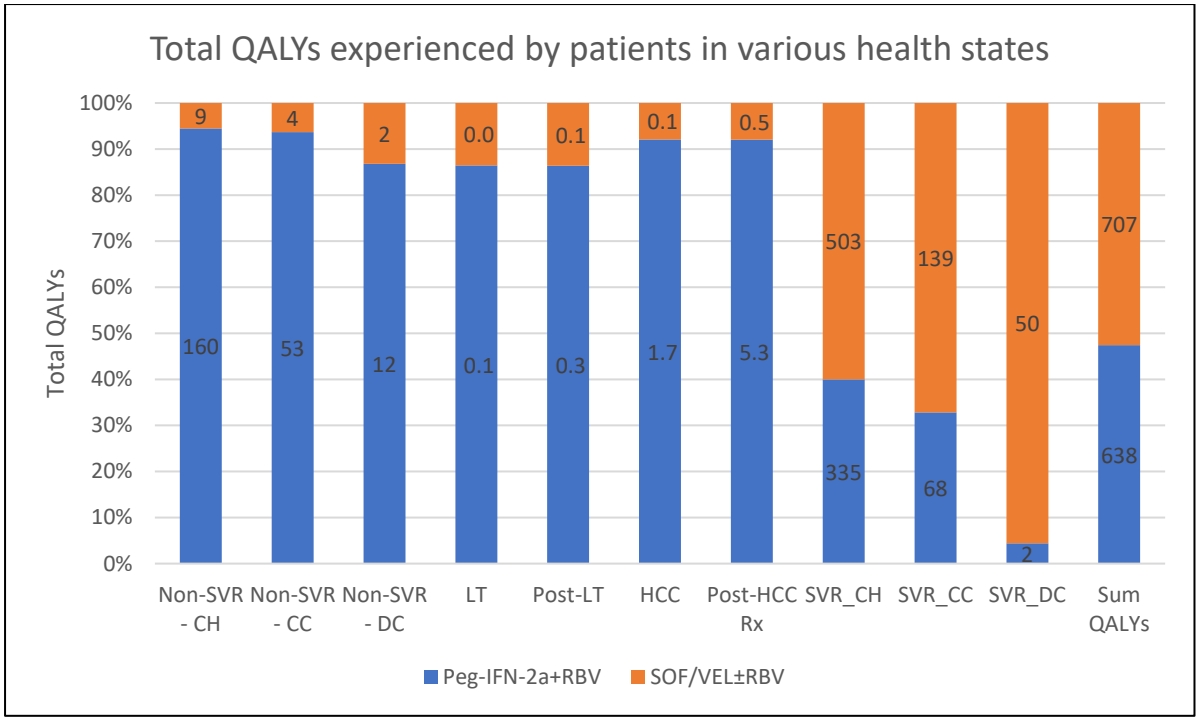

Figure 3. Total QALYs experienced by patients in various health states over 20 year management period/death. QALYs gained by treatment regimen were summed and stratified by the health state where QALYs were experienced. QALYs = Quality Adjusted Life Years, SVR = Sustained Virological Response, Non-SVR – CH = Patients who did not achieve SVR and had chronic hepatitis without cirrhosis during cycle, Non-SVR – CC = Patients who did not achieve SVR and had compensated cirrhosis during cycle, Non-SVR – DC = Patients who did not achieve SVR and had decompensated cirrhosis during cycle, LT = Patients underoing liver transplantation during cycle, Post-LT = Period after liver transplantation, HCC = Patients who had Hepatocellular Carcinoma during cycle, Post-HCC Rx = Period after management of Hepatocellular carcinoma, SVR-CH = Patients with SVR and chronic hepatitis without cirrhosis, SVR-CC = Patients with Sustained virological response and compensated cirrhosis, SVR-DC = Patients with Sustained virological response and decompensated cirrhosis, Sum QALYs = Total sum of QALYs by antiviral treatment regimen.

Table 5. Management costs over 20 years by health state

Long term management costs by health state	PEG-IFN-2α+RBV	SOF/VEL±RBV
	Chronic hepatitis	
Person-years treated	238	14
Monitoring and imaging	R310 181	R18 160
Liver biopsy	R217 684	R12 745
Subtotal	**R527 865**	**R30 904**
	Compensated cirrhosis	
Person-years treated	191	210
Monitoring and imaging	R542 039	R594 875
Liver biopsy‡	R291 766	R320 207
Subtotal	**R833 805**	**R915 082**
	Decompensated cirrhosis	
Person-years treated	25	72
Monitoring and imaging	R123 694	R209 581
DC complication hospitalization†	R4 269 (PY = 0.01)*	R9 691 (PY = 0.02)*
Liver transplantation†	R115 608 (PY = 0.12)*	R17 778 (PY = 0.02)*
Subtotal	**R243 571**	**R237 051**
	Hepatocellular carcinoma	
Person-years treated	5.5	0.5
HCC treatment†	R2 226 376	R183 329
Subtotal	R2 226 376	R183 329
Total long term management costs	**R3 831 617**	**R1 366 366**

*Note: Hospitalisation and liver transplantation due to decompensated cirrhosis (DC) experienced by a subgroup of those with decompensated cirrhosis.

‡As liver ultrasound (U/S) elastography and liver biopsies are not routinely performed, these procedures were limited to a small proportion of patients where the procedure was indicated (10% for liver U/S elastography and 5% for liver biopsies).

†Management costs associated with cirrhosis-related complications, liver transplantation, and hepatocellular carcinoma may appear lower than expected if the total duration of patient-years spent in that specific health state is less than one year.

Table 6. Final health outcomes by treatment group after 20 years of management and follow-up

Final health outcomes (n = 139 per treatment group)		
	PEG-IFN-2α+RBV - n (%)	**SOF/VEL±RBV - n (%)**
Sustained virological response	75 (54%)	133 (96%)
Decompensated cirrhosis	19 (14%)	3 (2%)
Hepatocellular carcinoma	6 (4%)	0.5 (0.3%)
Liver transplantation	0.1 (0.1%)	0.02 (0.01%)
Death - Liver-related	19 (14%)	10 (7.3%)

Price threshold analysis

The price threshold analysis found that treatment with SOF/VEL±RBV ceased to be cost-effective at a SOF/VEL drug cost of R41 064 (95% CI: R 39 879, R 42 308) per month when the WTP threshold was assumed to be R40 000/QALY (Figure 4). Using a cost-neutral approach, the affordability price threshold decreased to R 34 371 (95% CI: R 33 346, R 35 448), while a WTP equivalent to the 2022 Gross Domestic Product (GDP; 5 624 US Dollars = R101 803 per QALY) resulted in a monthly SOF/VEL cost threshold of R 51 405 (95% CI: R 49 974, R 52 907).

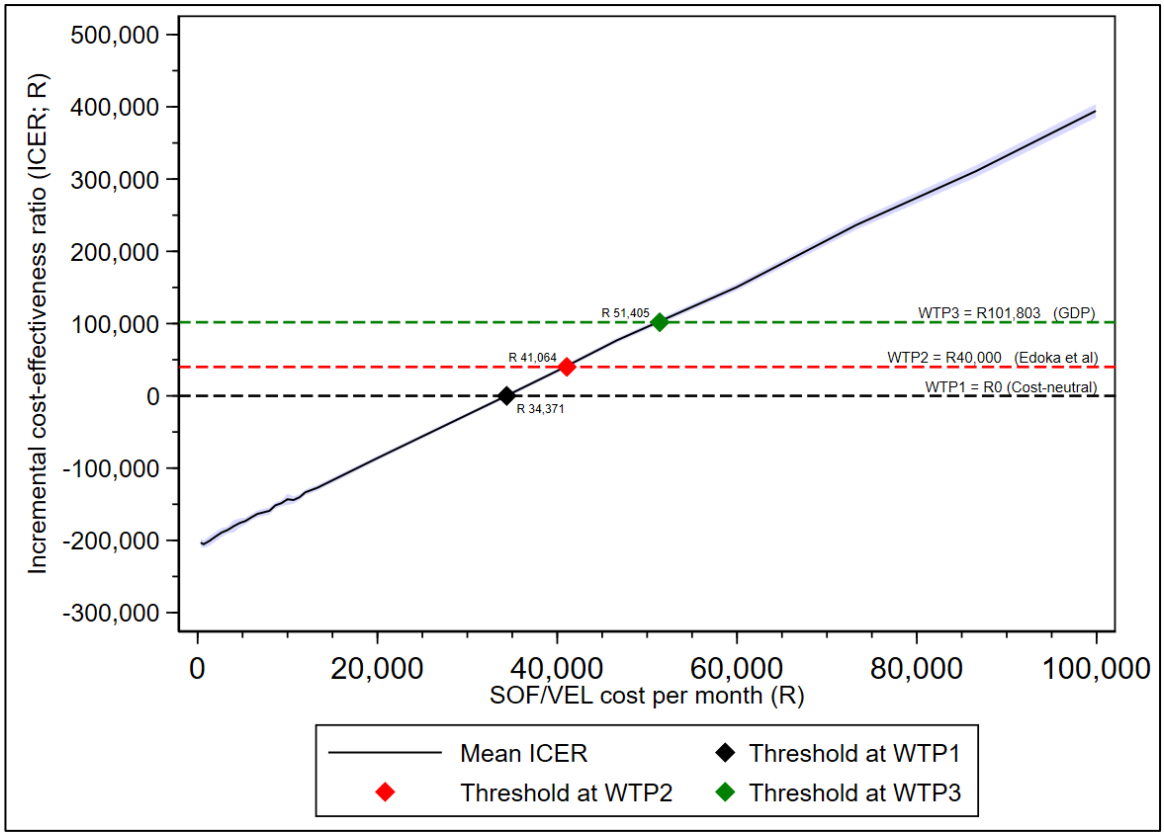

Figure 4. Price affordability threshold analysis with various Willingness To Pay (WTP) thresholds. A price threshold analysis was conducted to determine the cost at which SOF/VEL would no longer be considered cost-effective. Using a probabilistic model and 1 000 iterations of a Monte Carlo simulation, various price points relative to the current cost of sofosbuvir-velpatasvir were evaluated. The graph illustrates the relationship between the cost of SOF/VEL and the Incremental Cost-Effectiveness Ratio (ICER), indicating the point at which it becomes cost-ineffective. Confidence intervals were estimated using a bootstrap method to quantify uncertainty. WTP thresholds were used to calculate the threshold monthly of SOF/VEL assuming cost-neutrality (WTP1), at a WTP of R40 000 (Edoka et al), and at a WTP equivalent to the 2022 South Africa Gross Domestic Product (GDP) per capita of R101 803.

Sensitivity analyses

A univariate sensitivity analysis demonstrated that the model was most sensitive to the baseline prevalence of decompensated cirrhosis in the absence of antiviral therapy, the health utility gained in a state of SVR, drug costs for PEG-IFN-2α, costs associated with the management of HCC, and the rate that utilities were discounted during the model (Figure 5). Testing the model using the interquartile range bounds (25th and 75th centile values of assumed variable distributions) changed the ICER by a minimum and maximum of -21% and 11% respectively, indicating that the base-case cost-effectiveness was robust and not significantly impacted by the variability in model assumptions. The model was most sensitive to the management cost of HCC, resulting in a 21% decrease from the base-case ICER when the model parameter was replaced with the 75th centile (equivalent to a per-patient HCC treatment cost of R664 590). The results of the probabilistic sensitivity analysis were consistent with the base-case analysis and indicated that the cost-effectiveness remained consistent across different iterations (Figure 6). Furthermore, the probability of cost-effectiveness was predicted to be 100% across multiple WTP thresholds, up to R120 000 (Figure 7). The sensitivity analysis assessing the impact of viral genotype on the cost-effectiveness of SOF/VEL±RBV found similar results to the base-case analysis, indicating that treatment would be cost-effective regardless of the genotype being treated (Appendix 3). The sensitivity analysis by genotype found that the cost-effectiveness of SOF/VEL±RBV for the management of patients with hepatitis C viral genotypes 2 and 3 was moderated reduced, but still cost-saving. These differences in cost-effectiveness were largely due to moderately improved SVR rates for the PEG-IFN+RBV regimen in those with genotypes 2 and 3 compared to other genotypes. The sensitivity analysis testing the assumption that all patients eligible to receive the interferon-based intervention are treated found that the SOF/VEL±RBV intervention was cost-effective and cost-saving in the large majority of simulations, with an ICER of -23 068, and cost-effectiveness acceptability probabilities of 96% assuming a cost-neutral WTP threshold and 99.8% with a WTP threshold of R40,000 (Appendix 4 and Appendix 5).

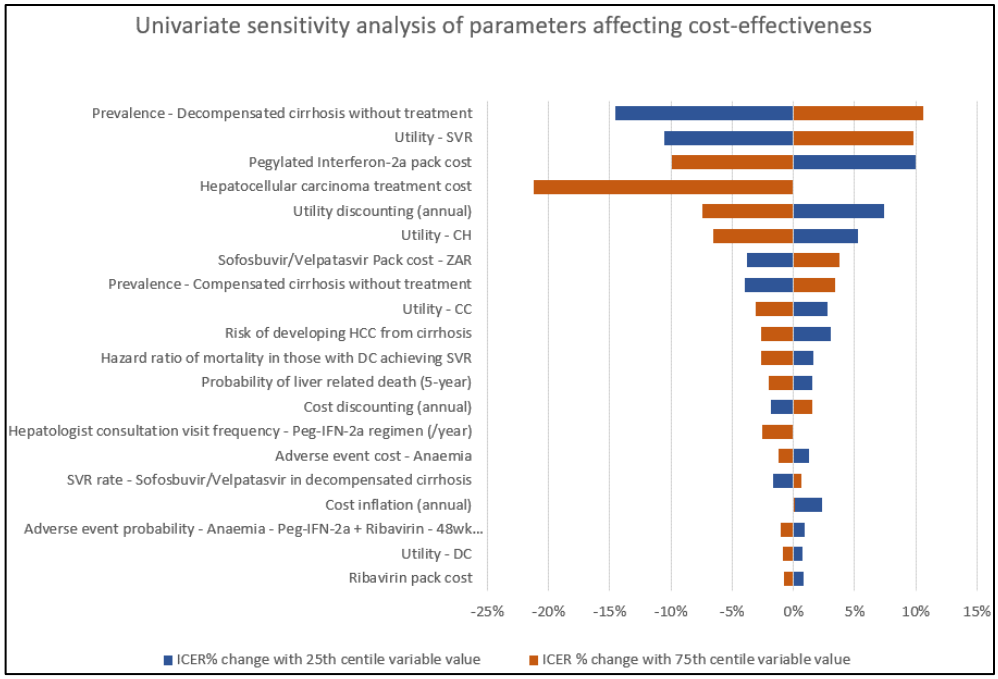

Figure 5*. Univariate sensitivity analysis tornado plot of the 20 most influential variables.* The diagram summarizes the results of a series of 1-way sensitivity analyses on the incremental cost effectiveness ratio (ICER). Each horizontal bar represents the percent change in ICER when the base-case model parameters are modified to the 25th or 75th centile values sampled from their distributions. The vertical line represents the

base-case ICER. SVR = Sustained virological response, CH = Chronic hepatitis, ZAR = South African Rands, CC = Compensated cirrhosis, HCC = Hepatocellular carcinoma, DC = Decompensated cirrhosis.

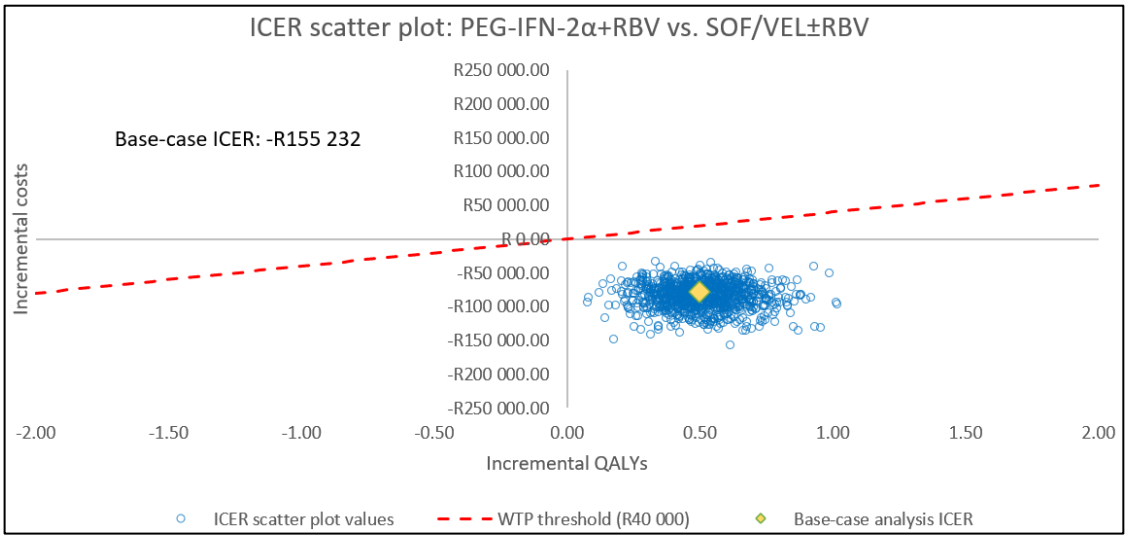

Figure 6. Incremental cost-effectiveness plane with base case and probabilistic sensitivity analysis of incremental cost-effectiveness ratios (ICER) for PEG-IFN-2α+RBV vs. SOF/VEL±RBV. A Monte Carlo simulation with 1 000 iterations was conducted for the probabilistic sensitivity analysis, with each blue circle representing one possible ICER. The diamond represents the base-case analysis, while the red, dashed line represents the willingness to pay threshold (WTP). PEG-IFN-2α+RBV = Pegylated interferon alfa-2α with ribavirin, SOF/VEL±RBV = Sofosbuvir/velpatasvir with or without ribavirin.

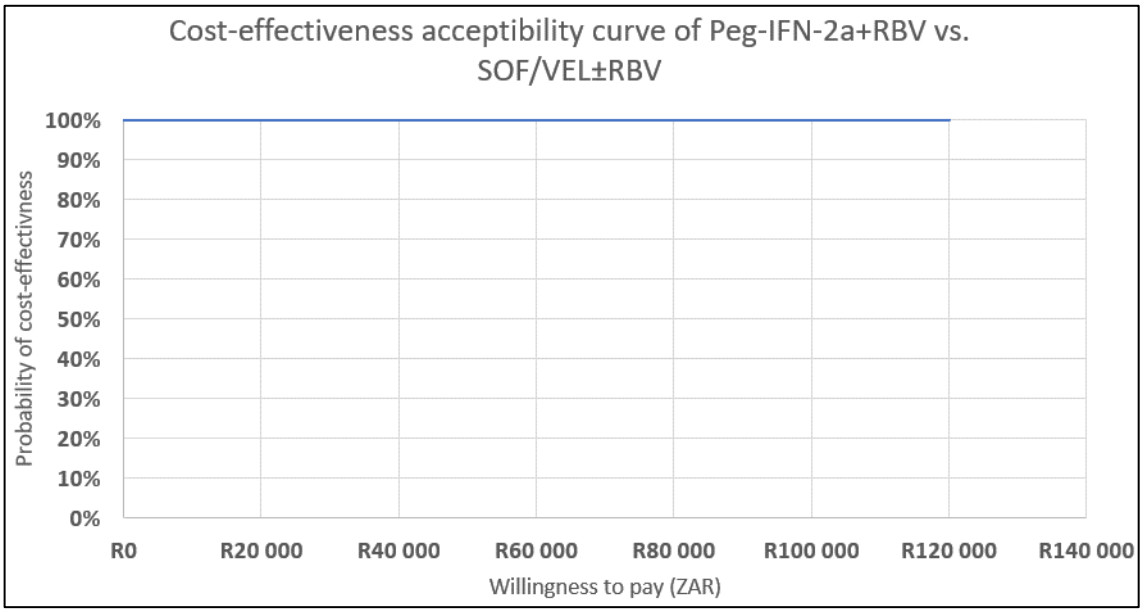

Figure 7. Cost-effectiveness acceptability curve of SOF/VEL with or without RBV. The results of 1 000 Monte Carlo simulations (probabilistic sensitivity analysis) in which all input variables are varied simultaneously based on the modelled input parameter distributions are reported. The graph shows the percentage of simulations in which PEG-IFN-2α+RBV was considered cost-effective compared with SOF/VEL±RBV, depending on the willingness to pay (WTP) threshold. All simulations were considered cost-effective up WTP thresholds of R120 000.

Budget impact analysis

The budget impact analysis revealed a consistent annual reduction in resource expenditure over a 30-year period as the uptake of SOF/VEL±RBV increased by 10% each year, leading to full implementation by year 10. In the first cohort (with 10% SOF/VEL±RBV uptake and costs assessed over 20 years), resource expenditure decreased by 6%. This downward trend in expenditure continued in subsequent cohorts, with the last cohort (treated with antiviral therapy starting at year 10 and managed until year 30) experiencing a 64% reduction in expenditure when SOF/VEL±RBV uptake was at 100% (Table 7, Figure 8). When compared with an alternative scenario where all patients were treated with Peg-IFN-2α+RBV (Table 7), there was a total reduction in resource expenditure of R63 200 336 over the 30-year period. SOF/VEL±RBV was also associated with reduced resource expenditure even when the proportion of patients treated with Peg-IFN-2α+RBV was reduced from 100% to 20%. The analysis indicated a potential reduction in resource expenditure of R26 213 075 over a 30 year period with incremental uptake of the DAA based regimen (Appendix 6 and Appendix 7).

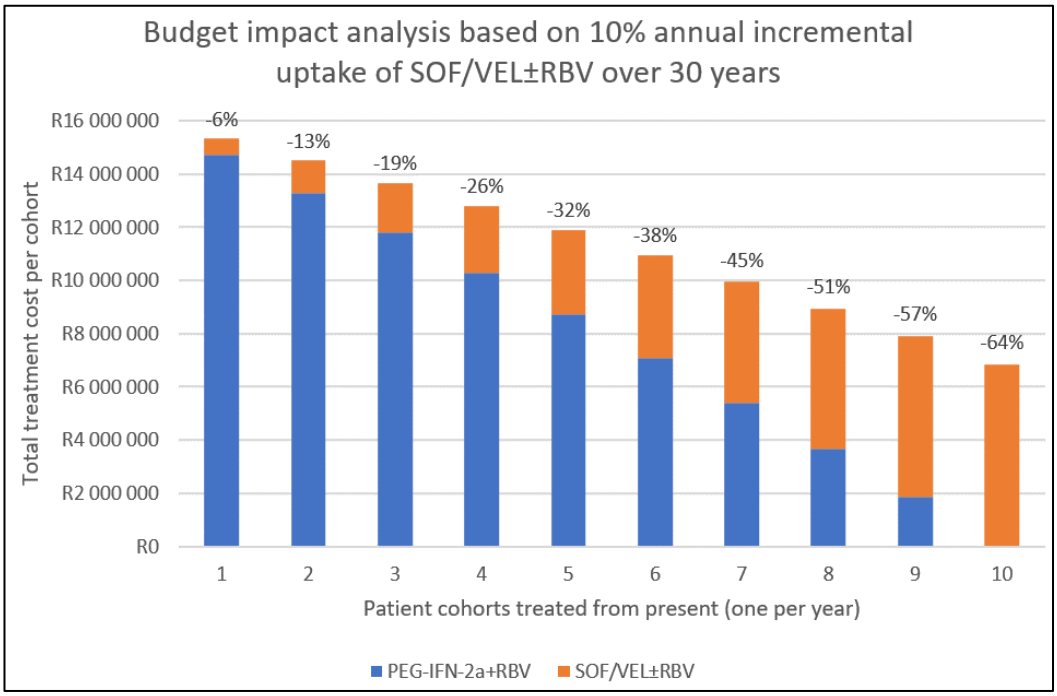

Figure 8. Budget Impact Analysis: 10% annual incremental uptake of SOF/VEL±RBV in Comparison to Treatment with Peg-IFN-2a+RBV of 10 cohorts. We compared the costs of treating 10 cohorts of patients with chronic hepatitis C infection using Peg-IFN-2α+RBV to the costs associated with incremental usage of SOF/VEL±RBV at a rate of 10% per year. Each cohort received antiviral treatment with further follow up for 20 years/up to death. The costs were adjusted for inflation and discounting. The percentage differences represent the differences in cost between 100% treatment with Peg-IFN-2α+RBV and the cost of treatment with incremental uptake of SOF/VEL±RBV. The total reduction in resource expenditure over 10 cohorts of treatment, totalling 30 years of follow up, amounted to R63 200 336. Peg-IFN-2α+RBV = Pegylated Interferon-2α+RBV, SOF/VEL±RBV = Sofosbuvir/Velpatasvir with or without ribavirin.

Table 7. Budget impact analysis of initial treatment costs using SOF/VEL±RBV assuming incremental intervention uptake of 10% per annum over 30 years

Treatment period from present (years)	Population size treated	%Incremental uptake of SOF/VEL±RBV	Treatment costs with PEG-IFN-2α+RBV only	Treatment costs with PEG-IFN-2α+RBV and SOF/VEL±RBV	Difference (%)
1 - 21	139	10%	R16 375 411	R15 330 826	-R1 044 586 (-6%)
2 - 22	141	20%	R16 635 687	R14 513 310	-R2 122 377 (-13%)
3 - 23	143	30%	R16 900 099	R13 665 933	-R3 234 166 (-19%)
4 - 24	144	40%	R17 168 714	R12 787 953	-R4 380 761 (-26%)
5 - 25	146	50%	R17 441 598	R11 878 611	-R5 562 988 (-32%)
6 - 26	148	60%	R17 718 820	R10 937 131	-R6 781 689 (-38%)
7 - 27	150	70%	R18 000 448	R9 962 723	-R8 037 725 (-45%)
8 - 28	152	80%	R18 286 552	R8 954 576	-R9 331 976 (-51%)
9 - 29	154	90%	R18 577 204	R7 911 865	-R10 665 339 (-57%)
10 - 30	156	100%	R18 872 475	R6 833 745	-R12 038 730 (-64%)
Total costs over 30 years			**R175 977 009**	**R112 776 672**	**-R63 200 336**

Note: The treatment costs of cohorts with chronic hepatitis C infection using both antiviral regimens were compared, with one cohort treated each year using PEG-IFN-2α+RBV alone, to the costs when SOF/VEL±RBV was increasingly used at a 10% annual uptake rate. The cohort managed from year 1 to 21, with a 10% uptake of SOF/VEL±RBV, incurred costs of R15 330 826. If this cohort had been treated solely with PEG-IFN-2α+RBV, there would have been a relative cost reduction of R1 044 586. The rightmost column in the table displays the difference and percent difference between the two treatment strategies, indicating the cost variations between cohorts receiving different treatments. Note that the management costs within each cohort, represented in each row, are incurred over a 20-year period. Finally, when the last cohort is treated using SOF/VEL±RBV starting at year 10 (with 100% implementation by then), the projected total savings would amount to R63 200 336 by year 30.

Conclusions

The analysis found that SOF/VEL±RBV was more cost-effective and cost-saving compared to PEG-IFN-2α+RBV in the treatment of patients with chronic hepatitis C. Importantly, this treatment was predicted to reduce morbidity and mortality due to disease related complications, as well as improve quality of life. These results were robust to sensitivity analyses. A price threshold analysis found that treatment with the DAA regimen would likely cease to be cost-effective at monthly costs between R39 879 and R42 308 per person with a WTP threshold of R40 000. Finally, the budget impact analysis estimated a reduction in annual treatment costs of approximately R63 million over 30 years with a 10% incremental uptake of the DAA-containing regimen. These findings have significant implications for direct-acting antivirals as a therapeutic option for patients with hepatitis C in this country.

Chronic hepatitis C infection is associated with significant morbidity, with patients often complaining of fatigue, reduced appetite, psychological distress and anxiety, and social isolation.[42] Treatment with SOF/VEL±RBV improved clinical outcomes and quality of life compared with the interferon-based regimens in this analysis. These agents are associated with high rates of SVR, an important predictor of improved clinical outcomes and quality of life, reduced risk of relapse, reduced mortality, and economic benefits. Perhaps even more important is their improved efficacy in patients with cirrhotic liver disease resulting in higher rates of SVR and hepatic function compared with interferon-based regimens, for whom interferon-based therapy is contraindicated. Untreated hepatitis C

infection is associated with a high risk of complications such as decompensated cirrhosis and hepatocellular carcinoma which reduce patient quality of life and incur significant costs for the patient, healthcare payer, and society. Patients treated with DAA's in this analysis were less likely to develop complications relating to decompensated cirrhosis, and were also significantly less likely to require liver transplantation or treatment for hepatocellular carcinoma. Recent reports also suggest that the treatment of patients with end stage liver disease is associated with a reduction in the rate of liver transplant waiting list registrations, an important potential advantage in a country with limited capacity for such interventions.[43, 44]

Despite the efficacy of these DAA agents, they have largely been unaffordable for many patients, with unsubsidised treatment costs potentially exceeding R1 million per patient. A previous study estimated that the treatment of an individual infected with hepatitis C in the United States in 2011 would cost approximately United States $205 760 at the full marketed cost.[45] This would be unaffordable on a population level in South Africa as the majority of these costs would be undertaken by the already over-burdened public sector. Therefore, securing long-term access to these drugs at an affordable cost under the voluntary license agreement will be critical.

The sensitivity analyses demonstrated the robustness of the developed model that was used in the base-case analysis. Among the variables tested in the univariate sensitivity analysis, the management cost of hepatocellular carcinoma had the greatest impact on the incremental cost-effectiveness ratio (ICER). This variation is primarily attributed to the uncertainty surrounding the actual cost of managing hepatocellular carcinoma in South Africa, where treatment options are limited and exhibit significant heterogeneity across healthcare settings. When the upper bound of the interquartile range was considered as the management cost (R664 590), the ICER decreased by 21%, indicating improved cost-effectiveness of SOF/VEL±RBV. This is largely due to the higher incidence of hepatocellular carcinoma associated with the interferon-based regimen, resulting in increased management costs, and further favouring the DAA regimen. The findings from the probabilistic sensitivity analyses align with those of the base-case analysis, indicating consistent cost-effectiveness results when different parameter values were sampled using Monte Carlo simulations. The cost-effectiveness acceptability analysis demonstrated that treatment with SOF/VEL±RBV had a high probability of acceptability across all simulations, encompassing a broad range of willingness-to-pay thresholds. Similarly, the sensitivity analysis by genotype found that SOF/VEL±RBV was cost-saving, regardless of genotype treated. The cost-effectiveness of the DAA regimen was marginally decreased among treated patients with genotypes 2 and 3, and this was largely due to the improved SVR rates in this subgroup, which has been observed in previous clinical trials of interferon-based therapy.[15, 46-49] Despite the marginally reduced cost-effectiveness associated with genotypes 2 and 3, the regimen remained cost-saving across all genotypes overall. These results have important implications for the use of SOF/VEL±RBV as a pan-genotypic therapy regimen. This finding highlights the potential benefits of using a pan-genotypic therapy, as it eliminates the need for genotype-specific treatments and associated costs for genotyping. This benefit could simplify the management of hepatitis C patients. By recommending a simplified treatment guideline, healthcare providers can administer the same treatment to patients regardless of their viral genotype, resulting in streamlined healthcare, reduced complexity associated with genotype-specific management, and improved resource allocation within healthcare systems. Together, these results support the cost-effectiveness findings of the SOF/VEL±RBV regimen, and reinforce the potential value of this intervention in the management of hepatitis C.

This analysis had a few important limitations: This analysis incorporated data from multiple sources, which may have introduced heterogeneity. Attempts were made to minimize heterogeneity, however, residual bias may still be present that could external validity. Additionally, the use of data from industrialised, upper income countries may not be entirely relevant for our healthcare and socioeconomic environment. Patients were assumed to be completely adherent to treatment, which may have overestimated the true effect of the intervention in a real-world scenario. This analysis did not incorporate indirect costs such as societal costs which often incur additional resource burdens for patients and may affect the relative cost-effectiveness. However, considering that the interferon-based therapy requires prolonged courses of treatment and engagement in healthcare, subcutaneous administration, and has a suboptimal efficacy and safety profile, cost-effectiveness of SOF/VEL may, in fact, be greater when such indirect costs are included. Lastly, other costs not included in this analysis such as those for consumable items or other components required for healthcare delivery were not included, and these may impact the cost-effectiveness results provided here.

In conclusion, this cost-utility analysis found that SOF/VEL±RBV was cost-effective, and cost-saving compared to PEG-IFN-2α+RBV in the treatment of chronic hepatitis C infection. Treatment with this DAA containing regimen was predicted to improve health outcomes and quality of life, while reducing mortality and treatment costs. This treatment should be considered for inclusion in the South African Essential Medicines List.

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Appendix 1. Model parameters and assumptions

Variable names	Distribution	Mean	Plausible min	Plausible max	References
Number of HCV genotypes	Constant	R1.00	1.00	3.00	Expert opinion
HCV genotype cost	Triangular	R2 370.00	R0.00	R2 500.00	[10]
Gross Domestic product per capita (SA)	Normal	R101 803.45	R30 000.00	R300 000.00	[50]
Willingness to pay (ZAR)	constant	$40 000.00	R0.00	R3 000 000.00	[39]
USD-ZAR rate	constant	R18.10	R1.00	R30.00	[51]
Pegylated Interferon-2α pack cost	Triangular	R1 361.20	R680.60	R2 041.80	[34]
Ribavirin pack cost	Triangular	R315.50	R252.40	R378.60	[34]
Sofosbuvir/Velpatasvir Pack cost - ZAR	Triangular	R6 661.00	R3 330.50	R9 991.50	(Riddin J, Personal communication, 2023)
Hepatitis C prevalence	binomial	1%	0.05%	2%	[52, 53]
SVR rate - Peg-IF-2α in Chronic hepatitis	Constant	65%	63%	68%	[15, 20-24]
SVR rate - Peg-IF-2α in Compensated cirrhosis	Constant	47%	44%	51%	[20, 21, 23-28]
SVR rate - Peg-IF-2α in Decompensated cirrhosis (Note: Patients did not receive treatment. Only here for reference)	Constant	24%	19%	30%	[29-31]
SVR rate - Sofosbuvir/Velpatasvir in Chronic hepatitis	Triangular	98%	97%	99%	[16-18]
SVR rate - Sofosbuvir/Velpatasvir in Compensated cirrhosis	Triangular	96%	93%	98%	[16-18]
SVR rate - Sofosbuvir/Velpatasvir in decompensated cirrhosis	Triangular	83%	74%	90%	[19]
Population - Total Adults	normal	43 200 000	30 000 000	60 000 000	[54, 55]
Public sector use proportion	binomial	80%	70%	95%	[54]

Population - Growth rate	binomial	1%	0.01%	5%	[56]
Access to care proportion	binomial	0.20%	0.1%	10%	[10, 57]
Hepatologist consultation cost (/hr)	Triangular	R706.00	R618.00	R772.00	[58]
Hepatologist consultation visit frequency - Peg-IFN-2α regimen (/year)	Count	4.00	2.00	10.00	[10]
Hepatologist consultation visit frequency - SOF/VEL±RBV regimen (/year)	Count	4.00	2.00	10.00	[10]
Liver transplantation cost	Triangular	R1 000 000.00	R500 000.00	R1 500 000.00	[59]
Hepatocellular carcinoma treatment cost	Triangular	R400 000.00	R250 000.00	R1 000 000.00	[60]
Prevalence of chronic hepatitis	Binomial	68%	34%	100%	[13]
Prevalence - Compensated cirrhosis without treatment	Beta	20%	5%	50%	[13]
Prevalence - Decompensated cirrhosis without treatment	Beta	12%	5%	50%	[14]
Probability Liver transplant receipt while in decompensated cirrhosis	Beta	5%	3%	8%	[43]
Utility - SVR	Beta	0.88	0.71	1.00	[61]
Utility - CH	Beta	0.86	0.72	0.95	[61]
Utility - CC	Beta	0.73	0.55	0.89	[61]
Utility - DC	Beta	0.60	0.45	0.81	[61]
Utility - LT	Beta	0.66	0.45	0.86	[61]
Utility - Post-LT	Beta	0.75	0.62	0.86	[61]
Utility - HCC	Beta	0.38	0.09	0.81	[61]
Utility - Post HCC Rx	Beta	0.55	0.35	0.62	[61, 62]
Cost discounting (annual)	Triangular	5%	0%	10%	[36]

Utility discounting (annual)	Triangular	5%	0%	10%	[36]
Cost inflation (annual)	Triangular	5.3%	0%	7%	[35]
Probability of liver related death (5-year)	Binomial	50%	10%	85%	[13, 63-65]
Adult proportion of total SA population	Binomial	72%	65%	80%	[55]
Proportion of population with diagnosed chronic Hepatitis C	constant	20%	0%	100%	[57]
Lab test costs - Full blood count	Triangular	R70.00	R35.00	R105.00	[66]
Lab test costs - Creatinine, Electrolytes, and urea cost	Triangular	R149.00	R74.50	R223.50	[66]
Lab test costs - Liver function test	Triangular	R224.42	R112.21	R336.63	[66]
Lab test costs - HCV viral load	Triangular	R664.34	R332.17	R996.51	[67]
Lab test costs - International normalized ratio	Triangular	R58.00	R29.00	R87.00	[66]
Lab test costs - ALT	Triangular	R55.00	R27.50	R82.50	[66]
Lab test costs - Differential count	Triangular	R39.00	R19.50	R58.50	[66]
Specialist consultation frequency - 24 week Peg-IFN Rx (/year)	Constant	9	4.5	13.5	[10]
Specialist consultation frequency - 48 week Peg-IFN Rx (/year)	Constant	10	1	20	[10]
Specialist consultation frequency - Sof/Vel Rx (/year)	Constant	5	1	20	[10]
Liver function test frequency - 24 week Peg-IFN Rx (/year)	Constant	8	1	20	[10]
Liver function tests frequency - 48 week Peg-IFN Rx (/year)	Constant	11	1	20	[10]
Liver function tests frequency - Sof/Vel Rx (/year)	Constant	3	1	20	[13]
Renal function tests frequency - 24 week Peg-IFN Rx (/year)	Constant	1	1	20	[10]
Renal function tests frequency - 48 week Peg-IFN Rx (/year)	Constant	1	1	10	[10]

Renal function tests frequency - Sof/Vel Rx (/year)	Constant	2	0	5	[13]
Full blood count frequency - 24 week Peg-IFN Rx (/year)	Constant	10	1	20	[10]
Full blood count frequency - 48 week Peg-IFN Rx (/year)	Constant	16	1	20	[10]
Full blood count frequency - SOF/VEL±RBV Rx (/year)	Constant	4	1	20	[13]
INR frequency - 24 week Peg-IFN Rx (/year)	Constant	3	1	20	[10]
INR frequency - 48 week Peg-IFN Rx (/year)	Constant	3	1	20	[10]
INR frequency - Sof/Vel Rx (/year)	Constant	2	1	20	[13]
HCV viral load frequency - 24 week Peg-IFN Rx (/year)	Constant	4	1	20	[10]
HCV viral load frequency - 48 week Peg-IFN Rx (/year)	Constant	5	1	20	[10]
HCV viral load frequency - Sof/Vel Rx (/year)	Constant	4	1	20	[10]
Failed SVR lab monitoring frequency - Chronic hepatitis (/year)	Count	1	2	3	[10]
Failed SVR lab monitoring frequency - Compensated cirrhosis (/year)	Count	2	3	4	[10]
Failed SVR lab monitoring frequency - Decompensated cirrhosis (/year)	Count	3	4	6	[10]
Failed SVR Liver biopsy frequency - Chronic hepatitis (/year)	Triangular	0.2	0.17	0.25	[10]
Failed SVR Liver biopsy frequency - Compensated cirrhosis (/year)	Triangular	0.33	0.25	0.5	[10]
Failed SVR Fibroscan frequency - Chronic hepatitis (/year)	Constant	1	1	1	[10]
Failed SVR Fibroscan frequency - Compensated cirrhosis (/year)	Constant	1	1	2	[10]
Failed SVR Fibroscan frequency - Decompensated cirrhosis (/year)	Constant	1	1	2	[10]

AFP frequency - Compensated and decompensated cirrhosis (/year)	Constant	2	2	2	[10]
Failed SVR lab monitoring cost	Constant	R501.42	0	R20 000.00	[10]
Fibroscan cost	Triangular	R750.00	R375.00	R1 125.00	[10]
Liver biopsy cost	Triangular	R90 000.00	R45 000.00	R135 000.00	[10]
AFP cost	Triangular	R120.00	R60.00	R180.00	[10]
Failed SVR - AFP frequency	Count	1	1	2	Expert opinion
Hospitalization rate for decompensated cirrhosis (/year)	Triangular	0.04%	0.00022	0.00066	[68, 69]
Hospitalization cost for decompensated cirrhosis	Triangular	R400 000.00	R200 000.00	R600 000.00	[10]
Hospitalization frequency for decompensated cirrhosis per patient (/year)	Count	1	1	9	[70]
Treatment duration - Peg-IFN-2α - Genotypes 1, 4, 5	Constant	48	48	48	[49]
Treatment duration - Peg-IFN-2α - Genotypes 2, 3	Constant	24	24	24	[49]
Treatment duration - SOF/VEL±RBV - All genotypes	Constant	1200%	12	12	[49]
Adverse event probability - Depression - Peg-IFN-2α + Ribavirin - 48wk regimen	Binomial	14%	0%	100%	[41]
Adverse event relative risk - Depression - Peg-IFN-2α + Ribavirin - 24wk regimen	Constant	0.775	0%	100%	[41]
Adverse event probability - Depression - Peg-IFN-2α + Ribavirin - 24wk regimen	Constant	11%	0%	100%	[41]
Adverse event Relative risk - Depression - Sofosbuvir/velpatasvir ± Ribavirin	Constant	0.2861	0%	100%	[41]
Adverse event Probability - Depression - Sofosbuvir/velpatasvir ± Ribavirin	Constant	4%	0%	100%	[41]
Adverse event probability - Anaemia - Peg-IFN-2α + Ribavirin - 48wk regimen	binomial	21%	0%	100%	[41]
Adverse event relative risk - Anaemia - Peg-IFN-2α + Ribavirin - 24wk regimen	Constant	0.97	0%	100%	[41]
Adverse event probability - Anaemia - Peg-IFN-2α + Ribavirin - 24wk regimen	Constant	21%	0%	100%	[41]

Adverse event Relative risk - Anaemia - Sofosbuvir/velpatasvir ± Ribavirin	Constant	0.69	0%	100%	[41]
Adverse event Probability - Anaemia - Sofosbuvir/velpatasvir ± Ribavirin	Constant	15%	0%	100%	[41]
Adverse event probability - Rash - Peg-IFN-2α + Ribavirin - 48wk regimen	Binomial	18%	0%	100%	[41]
Adverse event relative risk - Rash - Peg-IFN-2α + Ribavirin - 24wk regimen	Constant	1.03	0%	100%	[41]
Adverse event probability - Rash - Peg-IFN-2α + Ribavirin - 24wk regimen	Constant	19%	0%	100%	[41]
Adverse event Relative risk - Rash - Sofosbuvir/velpatasvir ± Ribavirin	Constant	0.5244	0%	100%	[41]
Adverse event Probability - Rash - Sofosbuvir/velpatasvir ± Ribavirin	Constant	10%	0%	100%	[41]
Adverse event cost - Depression	Triangular	R24 073.00	R12 036.50	R36 109.50	[41]
Adverse event cost - Anaemia	Triangular	R46 734.20	R23 367.10	R70 101.30	[41]
Adverse event cost - Rash	Triangular	R5 792.00	R2 896.00	R8 688.00	[41]
Genotype 1 prevalence	Constant	32%	0%	100%	[71]
Genotype 2 prevalence	Constant	3%	0%	100%	[71]
Genotype 3 prevalence	Constant	14%	0%	100%	[71]
Genotype 4 prevalence	Constant	15%	0%	100%	[71]
Genotype 5 prevalence	Constant	37%	0%	100%	[71]
Failed SVR - Hepatologist frequency (/year)	Constant	1	0%	100%	[41]
SVR with cirrhosis - Lab test costs	Constant	R563.42	R281.71	R845.13	[13]
SVR with cirrhosis - Lab test monitoring frequency	Count	2	1	2	[13]
SVR with cirrhosis - Fibroscan frequency	Count	1	1	2	[13]
Liver biopsy probability in cirrhosis	Binomial	5%	1%	10%	[72-74]
Proportion of patients with weight > 75 Kg	Binomial	70%	0%	100%	Expert opinion
Daily dose - Ribavirin - < 75 kg (mg)	Constant	1000	500	1500	[13]

Daily dose - Ribavirin - > 75 kg (mg)	Constant	1200	600	1800	[13]
Weekly dose - Pegylated interferon (mg)	Constant	0.18	0.09	0.27	[49]
Daily dose - SOF/VEL (mg)	Constant	500	250	750	[13]
Probability of having fibroscan	Triangular	0.1	0%	20%	Sonderup M. Personal communication. 2023
Relative risk of DC complication if SVR vs failed SVR	Triangular	75%	99%	60%	Expert opinion
Hazard ratio of mortality in those with DC achieving SVR	Triangular	20%	0.16	0.25	[75]
Hazard ratio of progressing from CC to DC if achieving SVR	Triangular	33%	0.26	0.42	[75]
5 year Probability of death after successful treatment of HCC (PHccRx to death_liver)	Triangular	60%	30%	90%	[76]
5 year Mortality rate after HCC dx (HCC to death_liver)	Triangular	82%	50%	95%	[77]
Mortality risk after liver transplantation	Triangular	20%	10%	30%	[78]
Risk of developing HCC from CH without cirrhosis	Triangular	2%	2%	5%	[79, 80]
Risk of developing HCC from cirrhosis	Binomial	4%	1%	10%	[13]
20-year mortality risk after successful LT	Triangular	47%	20%	80%	[81]

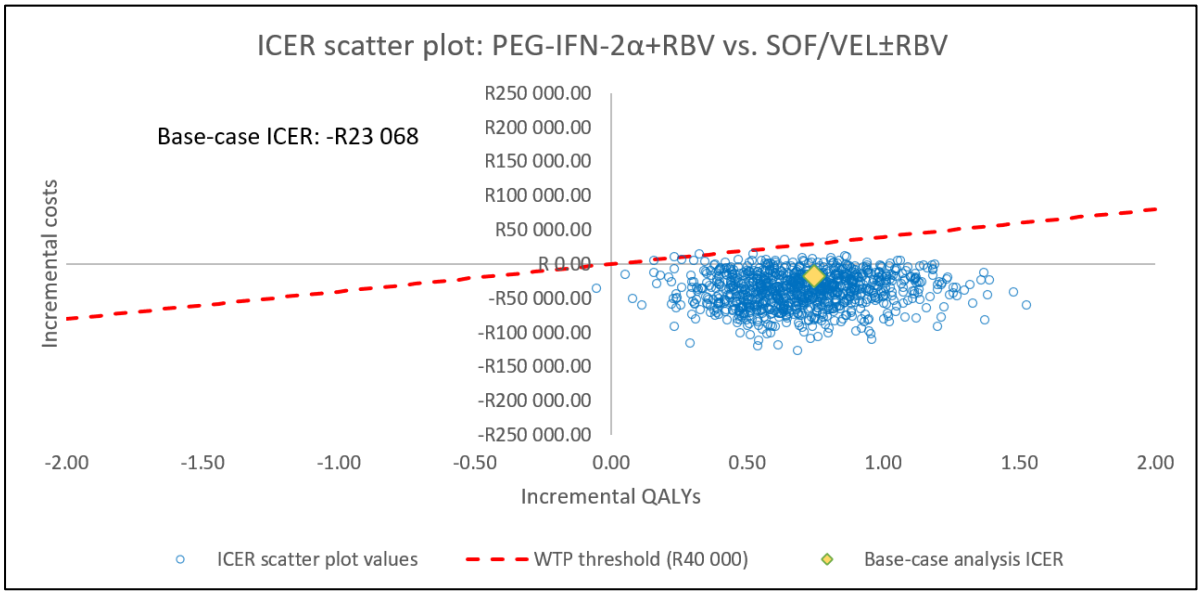
Appendix 2. Initial treatment costs by cost category and health state

Management modalities	PEG-IFN-2α+RBV	SOF/VEL±RBV
Chronic hepatitis		
Drug costs	R73 107	R19 983
Human resource costs	R2 590	R706
Lab test costs	R9 312	R6 395
Liver ultrasound and biopsy	R75	R75
Adverse event costs	R14 196	R555
Subtotal	R99 280	R27 714
Compensated cirrhosis		
Drug costs	R73 107	R23 580
Human resource costs	R2 590	R706
Lab test costs	R9 312	R6 395
Liver ultrasound and biopsy	R4 575	R4 575
Adverse event costs	R14 196	R8 442
Subtotal	R103 780	R43 698
Decompensated cirrhosis		
Drug costs	R0	R23 580
Human resource costs	R2 590	R706
Lab test costs	R9 312	R6 395
Liver ultrasound and biopsy	R4 575	R4 575
Adverse event costs	R0	R8 442
Subtotal	R16 476	R43 698
Total	**R90 243**	**R32 829**

Appendix 3. Sensitivity analysis of cost-effectiveness of SOF/VEL±RBV by genotype

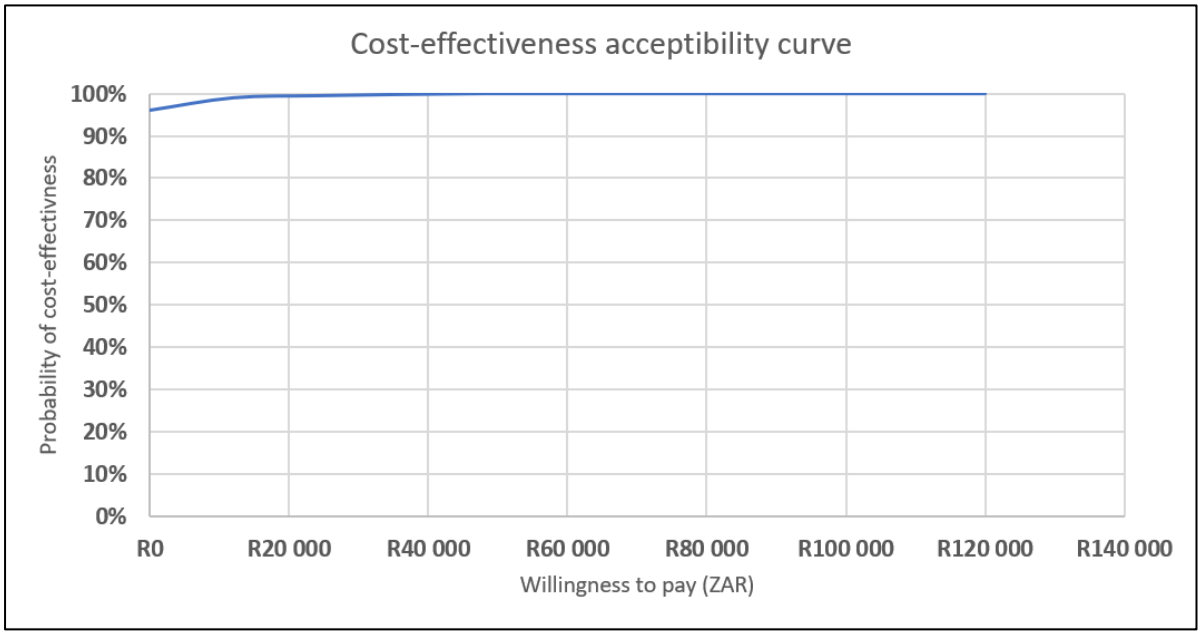
Genotypes	Incremental Costs	Incremental QALYs	ICER (95% CI)
Genotype 1	-R83 961	0.52	**-R 161 236 (-R161 451; -R161 021)**
Genotypes 2 & 3	-R36 425	0.28	**-R 128 634 (-R129 287; -R127 980)**
Genotypes 4, 5, & 6	-R86 187	0.48	**-R 179 712 (-R180 598; -R178 825)**

Appendix 4. The incremental cost-effectiveness plane depicts the probabilistic sensitivity analysis of incremental cost-effectiveness ratios (ICER) comparing PEG-IFN-2α+RBV versus SOF/VEL±RBV



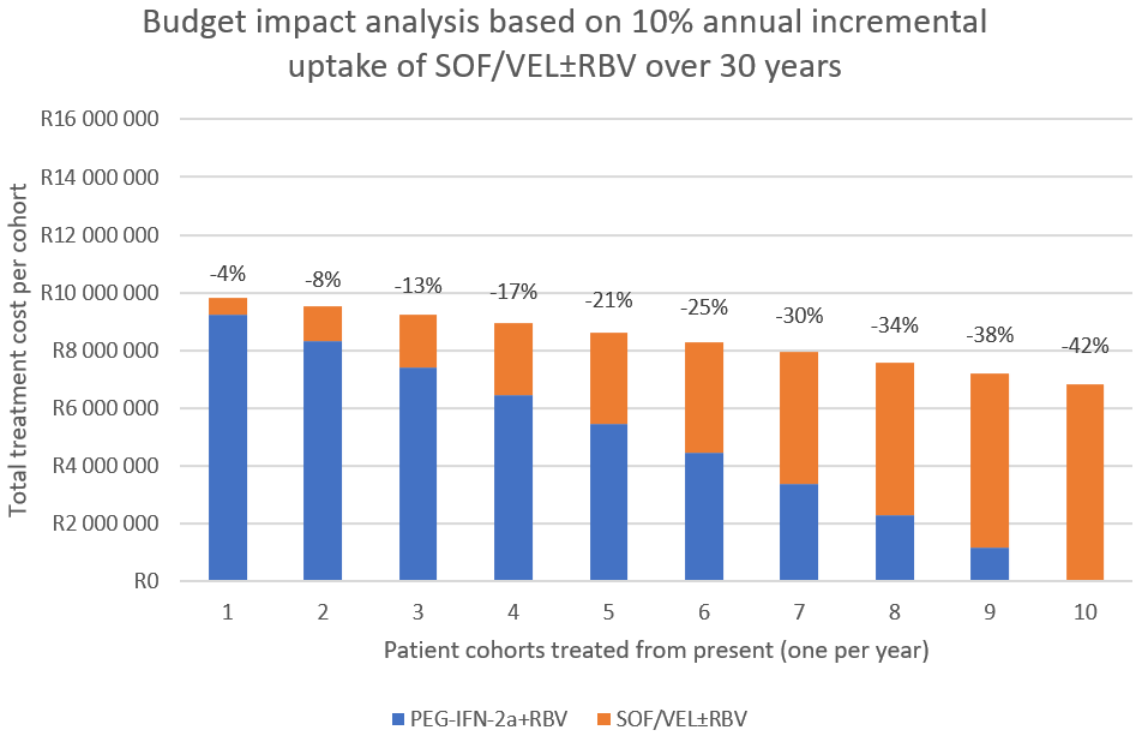
Varying assumptions of treatment proportions for patients assigned to Pegylated interferon alfa-2α with ribavirin (PEG-IFN-2α+RBV) therapy were tested using a Monte Carlo simulation with 1 000 iterations. Each blue circle represents one possible ICER. The diamond indicates the base-case analysis, considering a 20% treatment proportion of those eligible for PEG-IFN-2α+RBV. The red dashed line represents the willingness to pay threshold (WTP) of R40,000. The sensitivity analysis involved examining the cost-effectiveness of the Sofosbuvir/velpatasvir with or without ribavirin (SOF/VEL±RBV) regimen under different scenarios, where the proportion of patients eligible for PEG-IFN-2α+RBV therapy who actually received treatment ranged from 0% to 100%. The SOF/VEL±RBV intervention was cost-effective and cost-saving in the large majority of simulations conducted.

Appendix 5. Cost-effectiveness acceptability curve of SOF/VEL±RBV with varying assumptions of the treatment proportion of patients assigned to PEG-IFN-2α+RBV.



The cost-effectiveness acceptability graph presents the results of 1,000 Monte Carlo simulations conducted for the probabilistic sensitivity analysis. The analysis tested varying assumptions of the proportion of patients treated with Sofosbuvir/velpatasvir with or without ribavirin (SOF/VEL±RBV), ranging from 0% to 100%. The graph depicts the percentage of simulations in which SOF/VEL±RBV was considered cost-effective compared to Pegylated interferon alfa-2α with ribavirin (PEG-IFN-2α+RBV), based on different willingness-to-pay (WTP) thresholds. The simulations covered a broad range of WTP thresholds, up to R120,000. For the SOF/VEL±RBV intervention, the cost-effectiveness probability was 96% when a cost-neutral WTP threshold (R0/QALY) was considered. At a WTP threshold of R40 000/QALY, the cost-effectiveness probability increased to 99.8%.

Appendix 6. Budget Impact Analysis: 10% annual incremental uptake of SOF/VEL±RBV in Comparison to Treatment with Peg-IFN-2α+RBV of 10 cohorts with a 20% treatment proportion of patients assigned to receive Peg-IFN-2α+RBV



Budget Impact Analysis: 10% annual incremental uptake of SOF/VEL±RBV in Comparison to Treatment with Peg-IFN-2α+RBV of 10 cohorts. We compared the costs of treating 10 cohorts of patients with chronic hepatitis C infection using Peg-IFN-2α+RBV to the costs associated with incremental usage of SOF/VEL±RBV at a rate of 10% per year. The analysis tested the budget impact when the proportion of patients treated with Peg-IFN-2α+RBV was reduced to 20%. Each cohort received antiviral treatment with further follow up for 20 years/up to death. The costs were adjusted for inflation and discounting. The percentage differences represent the differences in cost between 100% treatment with Peg-IFN-2α+RBV and the cost of treatment with incremental uptake of SOF/VEL±RBV. The total reduction in resource expenditure over 10 cohorts of treatment, totalling 30 years of follow up, amounted to R26 213 075. Peg-IFN-2α+RBV = Pegylated Interferon-2α+RBV, SOF/VEL±RBV = Sofosbuvir/Velpatasvir with or without ribavirin.

Appendix 7. Budget impact analysis of initial treatment costs using SOF/VEL±RBV assuming incremental intervention uptake of 10% per annum over 30 years and a 20% treatment proportion of patients assigned to Peg-IFN-2α

Treatment period from present (years)	Population size treated	%Incremental uptake of SOF/VEL±RBV	Treatment costs with PEG-IFN-2α+RBV only	Treatment costs with Peg-IFN-2α+RBV and SOF/VEL±RBV	Difference (%)
1 - 21	42	10%	R11 484 759	R10 929 238	-R555 520 (-5%)
2 - 22	56	20%	R11 667 301	R10 538 601	-R1 128 700 (-10%)
3 - 23	72	30%	R11 852 744	R10 132 785	-R1 719 960 (-15%)
4 - 24	87	40%	R12 041 135	R9 711 406	-R2 329 729 (-19%)
5 - 25	102	50%	R12 232 520	R9 274 072	-R2 958 449 (-24%)
6 - 26	119	60%	R12 426 948	R8 820 382	-R3 606 565 (-29%)
7 - 27	135	70%	R12 624 465	R8 349 928	-R4 274 537 (-34%)
8 - 28	152	80%	R12 825 122	R7 862 290	-R4 962 832 (-39%)
9 - 29	170	90%	R13 028 968	R7 357 041	-R5 671 927 (-44%)
10 - 30	187	100%	R13 236 054	R6 833 745	-R6 402 309 (-48%)
Total costs over 30 years			**R123 420 016**	**R89 809 489**	**-R33 610 527**

Note: The management costs of cohorts with chronic hepatitis C infection using both antiviral regimens were compared, with one cohort treated each year using Peg-IFN-2α+RBV alone (assuming only 20% of patients eligible to receive therapy are actually treated), to the costs when SOF/VEL±RBV was increasingly used at a 10% annual uptake rate. For example, the cohort managed from year 1 to 21, with a 10% uptake of SOF/VEL±RBV, incurred costs of R10 929 238. If this cohort had been treated solely with PEG-IFN-2α+RBV, management costs would have amounted to R11 484 759 over a 20 year period. The rightmost column in the table displays the monetary difference and percent difference between the two treatment strategies, indicating a reduction in resource expenditure of R555 520 with 10% uptake of SOF/VEL±RBV. Note that the management costs within each cohort, represented in each row, are incurred over a 20-year period. When the last cohort is treated using SOF/VEL±RBV starting at year 10 (with 100% implementation), the total projected budget impact would amount to -R33 610 527 by year 30.