Modelling the cost-effectiveness of novel direct-acting antiviral (DAA) treatments in patients co-infected with hepatitis C and HIV

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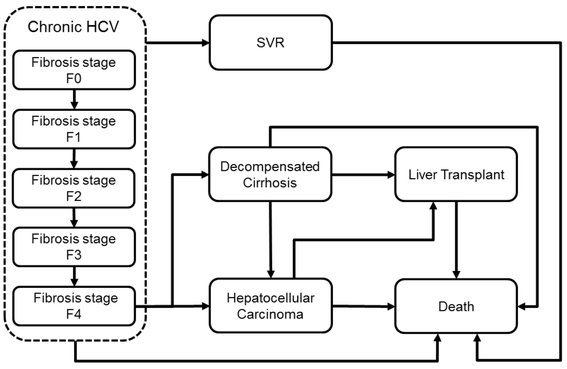
Introduction

- Compared to infection with chronic hepatitis C virus (HCV) alone, patients co-infected with human immunodeficiency virus (HIV) have an increased rate of disease progression, shorter survival, worse transplant outcomes and decreased treatment effectiveness [1-5].
- With the introduction of direct-acting antivirals (DAAs), the landscape of therapies available to treat HCV has rapidly expanded in recent years. These newly available HCV treatments have shown a propensity to achieve high rates of sustained virologic response (SVR) amongst HIV co-infected patients [6-8].
- The objective of this study was to compare the cost-effectiveness of novel DAA regimens daclatasvir (DCV) combined with sofosbuvir (SOF) and SOF combined with ribavirin (RBV) for the treatment of HCV genotypes 1 and 3, which predominate in the UK, in HIV co-infected patients who are treatment-naïve.

Methods

- A published Markov model [9-12] was used to estimate the relative cost-effectiveness of DCV+SOF versus SOF+RBV over a lifetime horizon in a cohort that had a mean age of 50 years and were 50% male.
- Patients were distributed evenly across METAVIR fibrosis stages F0 to F4 and may incur disease progression through fibrosis stages and on to end-stage liver disease (ESLD) complications and death (**Figure 1**).

Figure 1: Model flow diagram



- UK-specific HCV disease transition rates [13, 14] (**Table 1**) were combined with a HIV-specific multiplier (2.07) [15] to simulate fibrosis stage progression in this population.

Table 1: Disease state transition rates, costs and health utilities

Transition	Rate (SE)	Disease state	Utility (SE)	Cost (SE)
F0 to F1	0.077	F0-F1	0.77 (0.015)	£177 (35)
F1 to F2	0.092	F2-F3	0.66 (0.031)	£922 (98)
F2 to F3	0.145	F4	0.55 (0.054)	£1,464 (297)
F3 to F4	0.116	DC	0.45 (0.031)	£11,729 (1,954)
F4 to DC	0.039 (0.010)	HCC	0.45 (0.031)	£10,452 (2,456)
F4 to HCC	0.014 (0.010)	LTx (Yr 1)	0.45 (0.031)	£47,311 (6,843)
DC to HCC	0.014 (0.010)	LTx (Yr 2+)	0.67 (0.066)	£1,781 (457)
DC to LTx	0.030 (0.012)	Post-SVR (F0-F1)	0.82 (0.043)	£333 (62)*
HCC to LTx	0.030 (0.012)	Post-SVR (F2-F3)	0.72 (0.048)	£922 (98)*
DC to Death	0.130 (0.010)	Post-SVR (F4)	0.72 (0.048)	£1464 (288)*
HCC to Death	0.430 (0.030)	HIV (CD4 ≤200)	NA	£16,982 (1,495)
LTx (Yr 1) to Death	0.210 (0.046)	HIV (CD4 201-500)	NA	£9,305 (1,129)
LTx (Yr 2+) to Death	0.057 (0.012)	HIV (CD4 >500)	NA	£7,793 (1,364)

DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; LTx, liver transplant; SE, standard error; SVR, sustained virologic response; Yr, year.
* Applied in year of treatment only

- Disease state costs [16, 17] and health utility [14, 18-20] estimates (**Table 1**) were utilised to inform cost and quality of life outcomes.
- Upon initiation, HIV co-infected patients were distributed by their CD4 cell count (≤ 200 cells/µl: 43%; 201-500 cells/µl: 16%; >500 cells/µl: 41% [21]) with additional costs associated with the management of HIV, described in **Table 1**, applied dependent upon this distribution. Similarly, proportional reductions in health-related utility of 15%, 14% and 13% [22] were applied to each of the states, respectively. CD4 cell count was assumed not to change over the modelled horizon.
- Annual discount rates of 3.5% were applied. All-cause mortality was applied in line with published UK life tables [23] and rates observed in HIV co-infected subjects [24].
- Efficacy data was sourced from the ALLY-2 study for DCV+SOF [6] and the PHOTON-2 study for SOF+RBV [7,8], based upon the treatment-naïve populations and trial durations (**Table 2**).
- Therapy costs were sourced from MIMS [25], summarised in **Table 2**.
- Therapy-related adverse events and discontinuation were not modelled in this analysis.
- Cost-effectiveness was assessed through the accumulation of total costs, quality-adjusted life years (QALYs) and life years. Probabilistic sensitivity analysis was undertaken in order to assess parameter uncertainty associated with the analysis.
- Due to rates of SVR being derived from relatively small populations, an SVR threshold analysis was undertaken, where appropriate, to assess the lowest SVR of DCV+SOF that could be observed before the regimen in no longer is expected to be not cost-effective.

Table 2: Therapy profiles

Regimen	Genotype	Duration (weeks)	SVR			Total cost (£)
			N	% (SE)	Source	
DCV+SOF	1 3	12	80/83 6/6	96.4 (2.0) 100.0 (0.0)	[6]	59,500
SOF+RBV	1 3	24	182/226 52/57	80.5 (2.0) 91.2 (3.7)	[7,8]	71,572

DCV, daclatasvir; RBV, ribavirin; SE, standard error, SOF, sofosbuvir; SVR, sustained virologic response.

Results

- In HCV genotype 1 patients who are treatment-naïve, initiating therapy with DCV+SOF resulted in cost offsets of £12,693, QALY gains of 0.70 and life-year gains of 0.54 compared to SOF+RBV, as shown in **Table 3**. Similarly, amongst genotype 3 patients, cost offsets were £11,827, with QALY and life-year gains of 0.44 and 0.37, respectively.
- Resultant incremental cost-effectiveness ratios (ICERs) demonstrated that DCV+SOF is expected to dominate SOF+RBV.

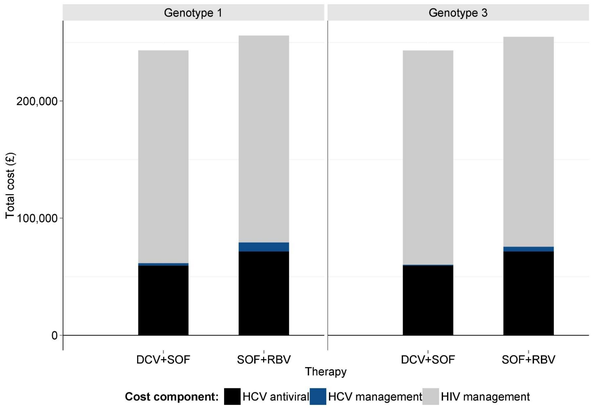
Table 3: Base case cost-effectiveness results

Regimen	Absolute			Incremental			Cost/ QALY (£)
	Cost (£)	QALYs	Life years	Cost (£)	QALYs	Life years	
Genotype 1							
DCV+SOF	243,145	12.48	19.08	-	-	-	-
SOF+RBV	255,837	11.78	18.54	-12,693	0.70	0.54	Dominant
Genotype 3							
DCV+SOF	243,003	12.64	19.20	-	-	-	-
SOF+RBV	254,830	12.20	18.83	-11,827	0.44	0.37	Dominant

DCV, daclatasvir; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response.

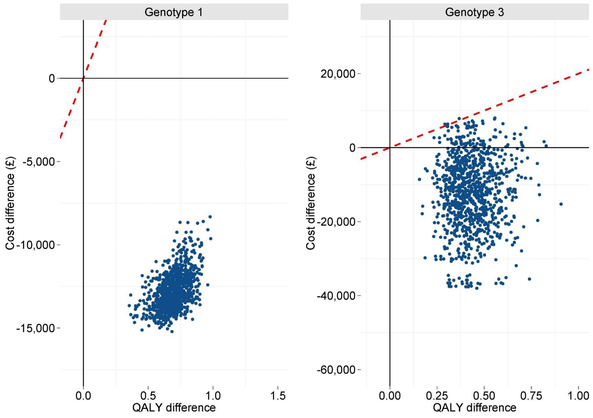
- **Figure 2** details the breakdown of total costs accumulated in each comparison. The majority of the total cost was attributed to the management of HIV, whilst the majority of cost offsets were attributable to the reduced cost of DCV+SOF compared to SOF+RBV (£12,072). HCV complications contributed to between 0.3% and 3.1% of the total costs across all arms.

Figure 2: Cost breakdown



- Results of the SVR threshold analysis demonstrated that the efficacy of DCV+SOF could fall from 96.4% to 66.9% in genotype 1 patients and from 100.0% to 78.2% in genotype 3 patients before becoming not cost-effective compared to SOF+RBV.
- Through probabilistic sensitivity analysis, shown in **Figure 3**, results demonstrated that all comparisons have a high likelihood (100% and 99.7%, for genotype 1 and genotype 3, respectively) of being cost-effective at the £20,000/QALY threshold.

Figure 3: ICER scatterplots



Conclusion

- In treatment-naïve patients co-infected with HIV and HCV genotypes 1 or 3, 12 weeks of treatment with DCV+SOF was predicted to be dominant (improved quality of life with decreased costs) compared to 24 weeks of SOF+RBV.
- Historically, efficacy of HCV treatments has been lower in patients co-infected with HCV and HIV. DCV+SOF has demonstrated high levels of efficacy in this patient population, and appears to be a cost-effective treatment option in treatment-naïve patients, based upon a willingness-to-pay threshold of £20,000/QALY.

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