Modelling the cost-effectiveness of the all-oral, direct acting antiviral (DAA) regimen daclatasvir + sofosbuvir in patients co-infected with hepatitis C virus (HCV) and HIV

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Introduction

- Compared to infection with the hepatitis C virus (HCV) alone, patients co-infected with the human immunodeficiency virus (HIV) have faster disease progression, decreased quality of life and increased rates of mortality [1-5].
- With the introduction of direct-acting antivirals (DAAs), the landscape of treatment for HCV has rapidly evolved.
- These novel treatments have shown high rates of sustained virologic response (SVR) in HIV co-infected patients [6-8].
- The objective of this study was to compare the cost-effectiveness of two novel, interferon-free DAA regimens: daclatasvir combined with sofosbuvir (DCV+SOF) and sofosbuvir combined with ribavirin (SOF+RBV) in the UK setting.

Methods

- In the absence of head-to-head data, indirect comparison of the clinical-effectiveness of treatment regimens was required. A systematic literature review was conducted to identify relevant trials for inclusion.
- The matching-adjusted indirect comparison (MAIC) method [9], which matches and adjusts for baseline characteristics of recruited patients, was used to compare efficacy data from the ALLY-2 and PHOTON-1/2 trials [6-8]: adjusted SVRs for 12 weeks of DCV+SOF and 24 weeks of SOF+RBV were 100% and 84.6%, respectively. Treatment-related adverse events and discontinuation were not extracted.
- Treatment costs were sourced from MIMS: DCV= £2,043.15; SOF = £2,915.24; and RBV = £66.95 per week [10].
- A published and validated Markov model for chronic hepatitis C (MONARCH; **Figure 1**) [11-14] was used to estimate the costs and benefits accumulated for each regimen over a lifetime horizon in a cohort with a mean age of 50 years and 50% male.
- The modelled cohort was evenly distributed across METAVIR fibrosis stages F0-F4 at initiation, with patients progressing through fibrosis stages and on to end-stage liver disease complications and death according to published rates (**Table 1**) [15, 16].
- As the cohort was co-infected with HIV, it was distributed according to CD4+ cell count (≤ 200 cells/µl: 43%; 201-500 cells/µl: 16%; > 500 cells/µl: 41% [17] [assumed not to change over the modelled horizon]), and a HIV-specific transition rate multiplier (2.07) was incorporated [18].

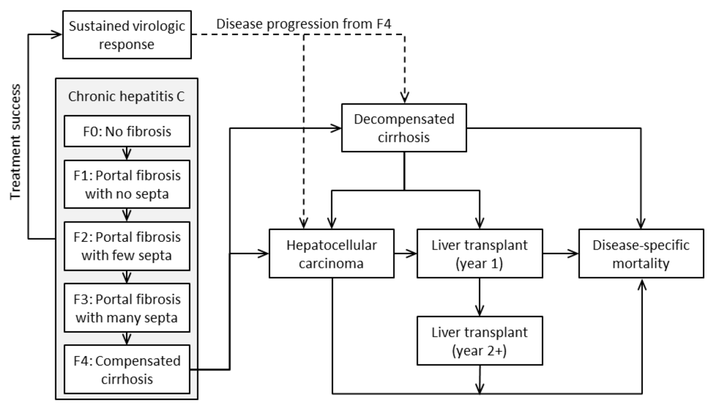

Figure 1: Model flow diagram

- Costs and utilities applied to chronic hepatitis C health states were UK-specific, and were discounted annually at 3.5% [15,19-22] (**Table 1**).
- Costs associated with HIV management and proportional reductions in health-related utility (15%, 14% and 13%) were applied based upon the starting distribution [17,23].
- The analysis was weighted per MAIC data (genotypes 1 & 4 = 56.5%; 2 = 16.5%; 3 = 27.0%).
- All-cause mortality was applied in line with published UK life tables [24] and rates observed in HIV co-infected subjects [25].

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

Transition	Rate (SE)	Health state	Utility (SE)	Cost, £ (SE)
F0 to F1	0.077	F0-F1	0.77 (0.015)	179 (35)
F1 to F2	0.092	F2-F3	0.66 (0.031)	932 (98)
F2 to F3	0.145	F4	0.55 (0.054)	1,480 (297)
F3 to F4	0.116	DC	0.45 (0.031)	11,859 (1,954)
F4 to DC	0.039 (0.010)	HCC	0.45 (0.031)	10,568 (2,456)
F4 to HCC	0.014 (0.010)	Liver transplant (year 1)	0.45 (0.031)	47,838 (6,843)
DC to HCC	0.014 (0.010)	Liver transplant (year 2+)	0.67 (0.066)	1,801 (457)
DC to liver transplant	0.030 (0.012)	Post-SVR (F0-F1)	0.82 (0.043)	337 (62)*
HCC to liver transplant	0.030 (0.012)	Post-SVR (F2-F3)	0.72 (0.048)	932 (98)*
DC to death	0.130 (0.010)	Post-SVR (F4)	0.72 (0.048)	1,480 (288)*
HCC to death	0.430 (0.030)	HIV (CD4+ ≤ 200)	NA	17,080 (1,495)
Liver transplant (year 1) to death	0.210 (0.046)	HIV (CD4+ 201-500)	NA	9,409 (1,129)
Liver transplant (year 2+) to death	0.057 (0.012)	HIV (CD4+ > 500)	NA	7,880 (1,364)

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

- Cost-effectiveness was estimated via the comparison of total costs, quality-adjusted life years (QALYs) and life years accumulated for each of the treatment regimens.
- Probabilistic sensitivity analysis (PSA) was undertaken to assess parameter uncertainty.
- Due to rates of SVR being derived from relatively small populations, an SVR threshold analysis was undertaken to assess the lowest SVR of DCV+SOF that could be observed before the regimen is no longer expected to be cost-effective.

Results

- Treatment with DCV+SOF resulted in reduced total costs and increased QALY gains compared to SOF+RBV, resulting in DCV+SOF dominating in terms of cost-effectiveness (**Table 2**).
- Predicted discounted total costs were £239,213 versus £250,014 for DCV+SOF and SOF+RBV, respectively.
- Predicted discounted QALYs were 11.56 versus 10.91 for DCV+SOF and SOF+RBV, respectively.
- The cost of HIV management was higher by £5,237 per person with DCV+SOF due to the increase in life expectancy (19.20 discounted years versus 18.64); however, there was a reduction in HCV management costs of £5,695 as a consequence of avoiding end-stage liver disease complications.

Table 2: Base case cost-effectiveness results

Regimen	Absolute			Incremental			Cost/ QALY (£)
	Cost (£)	QALYs	Life years	Cost (£)	QALYs	Life years	
DCV+SOF	239,213	11.56	19.20	-	-	-	-
SOF+RBV	250,014	10.91	18.64	-10,801	0.658	0.562	Dominant

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

- **Figure 2** details the breakdown of total costs, with most attributable to the management of HIV.
- The majority of cost savings can be attributed to the reduced cost of DCV+SOF compared to SOF+RBV (£11,269).
- HCV complication management contributed 0.33% and 2.52% of the total costs in respective arms.

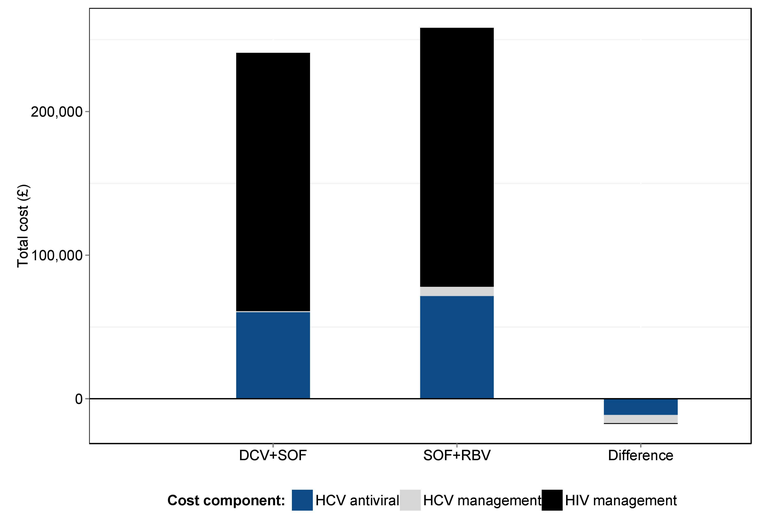

Figure 2: Cost breakdown

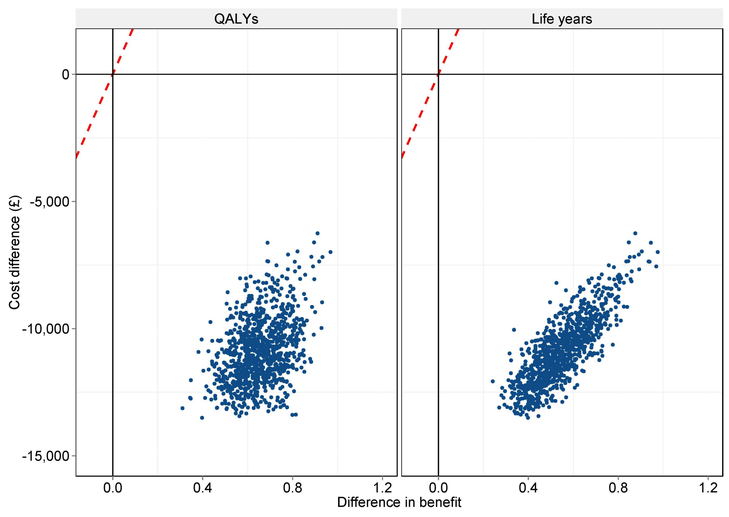

Figure 3: ICER scatterplots

- PSA demonstrated that all comparisons have a high likelihood (100%) of being cost-effective at the £20,000/QALY threshold (**Figure 3**).
- Results of the SVR threshold analysis demonstrated that the efficacy of DCV+SOF could fall to 72.4% before becoming not cost-effective compared to SOF+RBV at a £20,000/QALY threshold.

Conclusions

- In patients co-infected with HIV and HCV genotypes 1-4, 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.
- Cost-savings and QALY gains for the DCV+SOF regimen are driven by the shorter treatment duration and higher SVR, resulting in lower overall acquisition costs and fewer end-stage liver disease complications.

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Presented at the 18th Annual Congress of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), 7-11 November 2015, Milan, Italy.

This research was funded by Bristol-Myers Squibb Pharmaceuticals Ltd.

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