Supplemental Material

Online Supplementary Material:

Table EI: Modelled Population Characteristics

Characteristic	Patients, %	Source
CHC Subgroup		
General population	59.0	Authors' opinion[b]
HIV coinfected	7.0	Puoti et al 2019[1]
PWID	35.0	Authors' opinion[b]
HIV coinfected	13.9	Wiessing et al 2014[2]
Incarcerated	6.0	Authors' opinion[b]
HIV coinfected	10.3	Portuguese Ministry of Health[3]
Fibrotic Stage, monoinfected		Chen et al 2018[4]
F0	13.0[a]	
F1	30.5[a]	
F2	20.5[a]	
F3	19.0	
F4	17.0	
Fibrotic Stage, HIV coinfected		Cenderello et al 2016[5]
F0	10.7[a]	
F1	25.3[a]	
F2	17.0[a]	
F3	18.0	
F4	29.0	
Genotype, monoinfected		Puoti et al 2019[1]
GT1	67.0	
GT2	16.0	
GT3	10.0	
GT4	6.0	
GT other	0.1	
Genotype, HIV coinfected		Puoti et al 2019[1]
GT1	51.0	
GT2	4.0	
GT3	28.0	
GT4	18.0	
GT other	0	

CHC, chronic hepatitis C; PWID, people who inject drugs
[a]Distribution of F0/F1/F2 within the proportion F0-F2 reporting in the source were split based data observed by Dr. Fagiuoli in Lombardia from 2018-2019.
[b]Assuming the necessary resources are allocated to implement screening policies.

Table EII. Model Inputs for Chronic Hepatitis C Transition Probabilities With or Without SVR[6-9]

	Without SVR		With SVR	
Annual Risk of Development	**Monoinfected**	**HIV Coinfected**	**Monoinfected**	**HIV Coinfected**
NC→ CC			0	0
F0→ F1	0.117	0.123		
F1→ F2	0.085	0.113		
F2→ F3	0.121	0.124		
F3→ F4	0.115	0.116		
F3→ HCC	0.011	0.011	0	0
F4→ DC	0.030	0.042	0	0
F4→ HCC	0.050	0.070	0.010	0.014
DC→ LT	0.110	0.153	0.110	0.017
DC→ HCC	0.100	0.139	0.100	0.016
DC→ Liver death	0.090	0.125	0.090	0.014
HCC→ LT	0.200	0.278	0.200	0.278
HCC→ Liver death	0.430	0.599	0.430	0.599
LT (Year 1)→ Liver death	0.150	0.209	0.150	0.209
LT (Year 2+)→ Liver death	0.060	0.084	0.060	0.079

CC, compensated cirrhosis; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant; NA, not applicable; NC, non-cirrhotic; SVR, sustained virologic response

Table EIII. Model Inputs for SVRs by Genotype

Source	Genotype	SVR
Buggisch et al 2019[10]	GT3	56/58
Christensen et al 2017[11]	GT3	140/148
Soria et al 2019[12]	GT3	1202/1264 (319/237 for SOF/VEL)
Fagiuoli et al 2018[13]	GT3 CC	463/(496 + 9 + 3 + 21)
Mangia et al 2019[a][14]	GT1	547/558
	GT2	509/512
	GT3	198/204
	GT4	44/44
Degasperi et al 2019[15]	GT1	98/103
	GT2	17/18
	GT3	33/42
	GT4	14/16
Mangia et al 2019[b][16]	GT1	1595/1615
	GT2	1535/1553
	GT3	1646/1686
	GT4	238/239
	GT5-6	67/68
Weighted Average	GT1	2240/2276 = 98.4%
	GT2	2061/2083 = 98.9%
	GT3	2855/2994 = 95.4%
	GT4	296/299 = 99.0%
Total Weighted Average	**GT1-6**	**7200/7393 = 97.4%**

CC, compensated cirrhosis; SOF/VEL, sofosbuvir/velpatasvir.

Table EIV. Current Paradigm Time Between Steps

Steps	Weeks
DIAGNOSIS IN PRIMARY CARE/OR NON-HCV CoE	
1. Initial appointment to request anti-HCV and other tests	Start
2. Patient performs anti-HCV in a local lab	1 week
3. Appointment to present a positive anti-HCV test result and prescribe new tests	1 week
4. Patient performs additional tests	2 weeks
5. Appointment to present results of remaining tests	1 week
6. Referral to CoE and waiting for appointment	NC: 4 weeks in CoE with dedicated nurse (17.5% of population to be treated); 3 or 4 months if no dedicated slots CC: max 1 month
DIAGNOSIS IN CoE SPECIALIST CARE (HOSPITAL CONTEXT)	
7. First specialist appointment. Additional tests prescribed (including fibroscan)	defined as per previous step
8. Patient undergoes laboratory tests	2 weeks
9. Clinician enters patient data in Portal and requests authorization for treatment	Immediate
10. Waiting list (related to physician capacity)	max 4-6 weeks if NC 1 week if CC
TREATMENT	12 weeks
POST-TREATMENT FOLLOW-UP	F0-F2: 13 weeks (SVR12); F3+: 25 weeks (SVR24)

CC, compensated cirrhosis; CoE, Center of Excellence; NC, non-cirrhotic.

Table EV. Current Paradigm Number of Patients who are Retained in Care

	Retained in Care, n		
Step	**PWID[a]**	**Incarcerated[b]**	**General Population**
DIAGNOSIS IN PRIMARY CARE/OR NON- HCV CoE			
1. Initial appointment to request anti-HCV and other tests	1000	1000	1000
2. Patient performs anti-HCV in a local lab	891	950	950
3. Appointment to present a positive anti-HCV test result	830	950	950
4. Referral to CoE	810	950	950
5. Waiting for CoE specialist appointment	780	900	900
DIAGNOSIS IN CoE SPECIALIST CARE	745	850	850
TREATMENT	745	850	850
POST-TREATMENT FOLLOW-UP	745	850	850

CoE, Center of Excellence; LTFU, lost to follow up; PWID, people who inject drugs.
[a]Two modalities: either treated at PWID centers or accompanied to the CoE (approximately 20%) or referenced to the CoE without a peer. In the second case, LTFU is high and can go up to 20-30%. If treated at a PWID center, it is reasonable to assume that LTFU is similar to the General Population.
[b]There are two types of prisons - one is the typical prison where average length of stay is 3-5 months so they get fully treated in prison and LTFU is very low. The other is transitional prisons (while waiting for final sentence) and in these the average time is 6-8 weeks so there might not have time to complete treatment and here the LTFU is higher. The assumption is that the overall LTFU is the same as the General Population.

Table EVI. Model Inputs for Appointment and Laboratory Costs[17, 18]

Resource	Value
Appointments	
General practitioner	€20.66
Nurse[a]	€9.30
Specialist	€20.66
Laboratory test	
Complete blood count	€12.40
Anti HCV reflex	€9.60
Genotype	€82.00
APRI and FIB-4[b]	€59.20
Fibroscan	€64.00
Quantitative HCV-RNA	€60.40
Qualitative HCV-RNA	€43.60
HIV coinfection	
Anti-HIV antibodies	€14.00
HIV qualitative	€43.60
HIV quantitative	€60.40
HBV co-infection	
HBV DNA	€36.80
Anti-HBsAg antibodies	€9.60
Anti-HBeAg antibodies	€9.60
Biopsy	€120.00
Liver function panel[c]	€46.80
Bilirubin	€2.40
Sodium	€2.80
Creatinine	€10.40
Diabetes[d]	€41.20
Dyslipidemia[e]	€52.00
GGT	€2.80
Alkaline phosphatase	€2.40
Hemoglobin	
Hemoglobina	€2.40
Complete blood count and morphological exam	€4.80
Abdominal echogram	€60.00

APRI, aspartate amino-transferase to platelet ratio index; FIB-4, fibrosis-4; GGT, gamma glutamyl transpeptidase

[a]Calculated based on the following rational: 1. consider the hourly cost of physicians (gross wage + pension scheme) which is approximately €40 and proportionate it with the tariff (€

20,66): 20,66/40 = 0,51; 2. apply the 0,51 coefficient to the hourly cost of a nurse which is approximately € 18: 0,51 X 18 = € 9,30

[b]*Assumes 1 complete blood count and 1 liver panel*

[c]*Aspartate aminotransferase, alanine aminotransferase, total and fractioned bilirubin, serum cholinesterase, ammonium, GTT, alkaline phosphatase, total protein, blood protein electrophoresis, lipase, urine examination*

[d]*Glucose, calcium, serum albumin, sodium, potassium, bicarbonates, chloride, azotemia, creatinine, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, bilirubin*

[e]*Total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, lipidogram, apolipoproteins A and B, homocysteine, C reactive protein*

Table EVII. Model Inputs for Annual Cost by Fibrotic State and Advanced Liver Disease[19]

Health State	Annual Cost (2019)
F0-F1-F2	€171.99
F3	€1,355.92
F4	€1,355.92
Follow-up after SVR (F0/F2)	€114.15
DC	€5,924.60
HCC	€20,000.00
LT Year 1	€62,648.00
LT Year 2+	€4,729.00

DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant; SVR, sustained virologic response

Table EVIII. Base Case Values for Model Parameters and Their Respective Ranges Used for the Deterministic Sensitivity Analyses of Progression to Advanced Liver Disease and Costs.

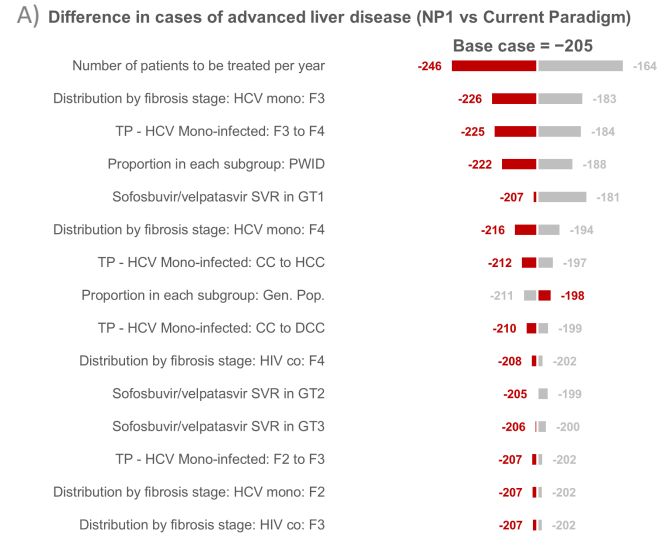
Parameters	Base Case Value	Low Value	High Value
Number of patients to be treated per year	30,000	24000	36000
Proportion in each subgroup			
PWID	0.353	0.2824	0.4236
General Population	0.586	0.4688	0.7032
Incarcerated	0.061	0.0488	0.0732
Proportion HIV co-infected			
PWID	0.139	0.1112	0.1668
General Population	0.07	0.056	0.084
Incarcerated	0.103	0.0824	0.1236
Distribution by fibrosis stage			
HCV monoinfected: F0	0.13	0.13	0.13
HCV monoinfected: F1	0.305	0.305	0.305
HCV monoinfected: F2	0.205	0.205	0.205
HCV monoinfected: F3	0.19	0.19	0.19
HCV monoinfected: F4	0.17	0.17	0.17
HIV co-infected: F0	0.107	0.107	0.107
HIV co-infected: F1	0.253	0.253	0.253
HIV co-infected: F2	0.17	0.17	0.17
HIV co-infected: F3	0.18	0.18	0.18
HIV co-infected: F4	0.29	0.29	0.29
F0 to F2 with comorbidities	0.15	0.12	0.18
Genotype distribution			
HCV monoinfected: GT1	67%	0.67	0.67
HCV monoinfected: GT2	16%	0.16	0.16
HCV monoinfected: GT3	10%	0.1	0.1
HCV monoinfected: GT4	6%	0.06	0.06
HCV monoinfected: other	1%	0.01	0.01
HIV co-infected: GT1	51%	0.51	0.51
HIV co-infected: GT2	4%	0.04	0.04
HIV co-infected: GT3	28%	0.28	0.28
HIV co-infected: GT4	17%	0.17	0.17
HIV co-infected: other	0%	0	0
Transition probability			
HCV monoinfected: F0 to F1	0.117	0.0936	0.1404
HCV monoinfected: F1 to F2	0.085	0.068	0.102
HCV monoinfected: F2 to F3	0.121	0.0968	0.1452
HCV monoinfected: F3 to F4	0.115	0.092	0.138
HCV monoinfected: F3 to HCC	0.011	0.0088	0.0132

HCV monoinfected: CC to DC	0.03	0.024	0.036
HCV monoinfected: CC to HCC	0.05	0.04	0.06
HCV monoinfected: DC to LT	0.11	0.088	0.132
HCV monoinfected: DC to HCC	0.1	0.08	0.12
HCV monoinfected: DC to Liver death	0.09	0.072	0.108
HCV monoinfected: HCC to LT	0.2	0.16	0.24
HCV monoinfected: HCC to Liver death	0.43	0.344	0.516
HCV monoinfected: LT to Liver death	0.15	0.12	0.18
HCV monoinfected: LT (Year 2+) to Liver death	0.079	0.0632	0.0948
HCV monoinfected: F4 SVR to DC	0	0	0
HCV monoinfected: F4 SVR to HCC	0.01	0.008	0.012
HIV co-infected: F0 to F1	0.123	0.0984	0.1476
HIV co-infected: F1 to F2	0.113	0.0904	0.1356
HIV co-infected: F2 to F3	0.124	0.0992	0.1488
HIV co-infected: F3 to F4	0.116	0.0928	0.1392
HIV co-infected: F3 to HCC	0.011	0.0088	0.0132
HIV co-infected: CC to DC	0.042	0.0336	0.0504
HIV co-infected: CC to HCC	0.07	0.056	0.084
HIV co-infected: DC to LT	0.153	0.1224	0.1836
HIV co-infected: DC to HCC	0.139	0.1112	0.1668
HIV co-infected: DC to Liver death	0.125	0.1	0.15
HIV co-infected: HCC to LT	0.278	0.2224	0.3336
HIV co-infected: HCC to Liver death	0.599	0.4792	0.7188
HIV co-infected: LT to Liver death	0.209	0.1672	0.2508
HIV co-infected: LT (Year 2+) to Liver death	0.06	0.048	0.072
HIV co-infected: F4 SVR to DC	0	0	0
HIV co-infected: F4 SVR to HCC	0.014	0.0112	0.0168
Cost			
Complete blood count	12.4	9.92	14.88
HCV ab	9.6	7.68	11.52
Anti HCV reflex	70	56	84
Quantitative HCV-RNA	60.4	48.32	72.48
Qualitative HCV-RNA	43.6	34.88	52.32
Genotype	82	65.6	98.4
Fibroscan	64	51.2	76.8
APRI and FIB-4[b]	59.2	47.36	71.04
Anti-HIV antibodies	14	11.2	16.8
HIV quantitative	60.4	48.32	72.48
Anti-HBsAg & HBeAg	19.2	15.36	23.04
HBV DNA	36.8	29.44	44.16
Biopsy	120	96	144

Liver function panel	46.8	37.44	56.16
Bilirubin	2.4	1.92	2.88
Sodium	2.8	2.24	3.36
Creatinine	10.4	8.32	12.48
Diabetes	41.2	32.96	49.44
Dyslipidemia	52	41.6	62.4
GGT	2.8	2.24	3.36
Alkaline phosphatase	2.4	1.92	2.88
Hemoglobin / Complete blood count and morphological exam	7.2	5.76	8.64
Abdominal echogram	60	48	72
General practitioner visit	20.66	16.528	24.792
Specialist visit	20.66	16.528	24.792
Nurse visit	9.3	7.44	11.16
Specialist wage per hour	49	39.2	58.8
Cost to patient			
Test outside specialist visit	36.15	28.92	43.38
Specialist	0	0	0
Opportunity cost per visit	63.56	50.848	76.272
Health state costs			
F0 to F3	443.0101	354.408096	531.6121446
CC	1355.92	1084.736	1627.104
DC	5924.6	4739.68	7109.52
HCC	20000	16000	24000
LT	62648	50118.4	75177.6
LT (Year 2+)	4729	3783.2	5674.8
Sofosbuvir/velpatasvir SVR in GT1	0.984	0.7872	1
Sofosbuvir/velpatasvir SVR in GT2	0.989	0.7912	1
Sofosbuvir/velpatasvir SVR in GT3	0.954	0.7632	1
Sofosbuvir/velpatasvir SVR in GT4	0.99	0.792	1
Sofosbuvir/velpatasvir SVR in other GT	0.974	0.7792	1

APRI, aspartate amino-transferase to platelet ratio index; CC, compensated cirrhosis; DC, decompensated cirrhosis; FIB-4, fibrosis-4; GGT, gamma glutamyl transpeptidase; HCC, hepatocellular carcinoma; LM, liver-related mortality; LT, liver transplant; PWID, people who inject drugs; SVR, sustained virologic response.

Figure E1: Deterministic sensitivity analysis progression to advanced liver disease model. Data are for the current paradigm compared with A) new paradigm 1 (NP1), and B) new paradigm 2 (NP2) after 5 years. CC, compensated cirrhosis; DC, decompensated cirrhosis; GTn, HCV genotype; HCC, hepatocellular carcinoma; LM, liver-related mortality; SVR, sustained virologic response; TP, transition probability.



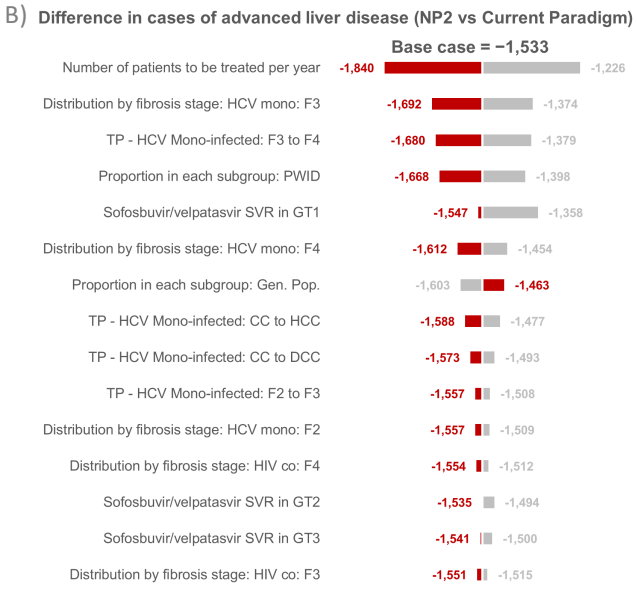


Figure E2: Deterministic sensitivity analysis cost model. Data are for the current paradigm compared with A) new paradigm 1 (NP1), and B) new paradigm 2 (NP2) after 5 years. APRI, aspartate amino-transferase to platelet ratio index; CC, compensated cirrhosis; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; PWID, people who inject drugs; SVR, sustained virologic response; TP, transition probability.

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