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Long-term clinical benefits of Sofosbuvir-based direct antiviral regimens for patients with chronic hepatitis C in Central and West Africa

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1 **Title: Long-term clinical benefits of Sofosbuvir-based direct antiviral regimens for**
2 **patients with chronic hepatitis C in Central and West Africa**

3

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26

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36 **Abbreviations:** CC, Compensated cirrhosis; CHC, Chronic hepatitis C; CI, Confidence Intervals;
37 DAAs, Direct Acting Antivirals; DC, Decompensated cirrhosis; GDP, Gross domestic product; HCC,
38 Hepatocellular carcinoma; HCV, Hepatitis C virus; HE, Health expenditures; HIC, High-income
39 countries; LIC, Low-income countries; LY, Life-years; LYS, Life-years saved; OOP, out-of-pocket
40 payments; PCR, polymerase chain reaction; SSA, Sub-Saharan Africa; SVR, Sustained virologic
41 response; WHO, World Health Organization.

42

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62

63 **Ethics approval statement**

64 The national Ethic Committees of the three study countries (Cameroon, Côte d'Ivoire and Senegal)
65 approved the protocol for the study.

66

67 **Patient consent statement**

68 Not applicable.

69

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72

73 **ABSTRACT (word count: 249)**

74 **Background:** In Sub-Saharan Africa, chronic hepatitis C (CHC) is a major public health issue. We
75 estimated the long-term clinical benefits of treating CHC with sofosbuvir-based regimens in Cameroon,
76 Côte d'Ivoire and Senegal using Markov model combining data from the literature with estimates of
77 direct antiviral agents (DAAs) effectiveness in West and Central Africa.

78 **Methods:** Disease progression was simulated with and without treatment in fictive cohorts of patients
79 "diagnosed" with CHC in Cameroon (n=3224), Côte d'Ivoire (n=9748) and Senegal (n=6358). Lifetime
80 treatment benefits were assessed using i) life-years saved (LYS), ii) life-years (LY) avoided in
81 compensated cirrhosis (CC), decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC), iii)
82 comparison of the proportions of patients at each disease stage with and without treatment. Probabilistic
83 and determinist sensitivity analyses were performed to address uncertainty.

84 **Results:** Sofosbuvir-based treatment would save [mean, 95% Confidence Intervals] 3.3 (2.5;5.7) LY
85 per patient in Cameroon, 2.7 (2.1;4.8) in Côte d'Ivoire and 3.6 (2.8;6.3) in Senegal. With treatment,
86 approximately 6% (1%) of the patients still alive in each of the study countries would be in the CC (DC)
87 health state 11 (15) years after CHC diagnosis, versus 15% (5%) without treatment. Scenario analysis
88 showed earlier diagnosis and treatment initiation would dramatically improve LYS and morbidity.

89 **Conclusion:** Sofosbuvir-based treatment could significantly reduce CHC-related mortality and help
90 control CHC-related liver disease progression in West and Central Africa. However, the goal of disease
91 elimination necessitates a substantial decrease in DAAs prices, greater political commitment, and
92 increases in both national and external health expenditures.

93

94 **Keywords:** hepatitis C; direct-acting antiviral agents (DAAs); markov simulation; low-income
95 countries; Africa.

96

97 **Lay summary**

98 We estimated that the treatment of chronic hepatitis C (CHC) with direct antiviral agents could lead to
99 a 75% reduction in the number of CHC-related liver complications 15 years after CHC diagnosis, and a
100 73% reduction in mortality in West and Central Africa. Mortality and morbidity outcomes could be
101 further significantly improved if early diagnosis and treatment were implemented. Our findings provide
102 a strong argument for universal treatment of CHC patients using DAAs in West and Central Africa.

103

104 INTRODUCTION

105 Viral hepatitis is a global public health issue affecting 325 million people in 2015, including 71 million
106 with the hepatitis C virus (HCV)¹. The burden of HCV infection is especially high in Sub-Saharan Africa
107 (SSA), which accounts for 14% of the total number of people infected with HCV worldwide². HCV
108 viremic prevalence is unevenly distributed in this region, with the highest prevalence rates in Central
109 (2.1%) and West (1.3%) Africa².

110 HCV causes both acute and chronic infection. While acute infection is usually asymptomatic and
111 resolved spontaneously without treatment in 15-45% of infected persons, 60–80% of those infected
112 develop chronic hepatitis C (CHC)³. In the absence of timely diagnosis and adequate treatment, CHC
113 may progress to liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC)⁴. In addition, the risk of
114 mortality associated with liver disease is high, especially in SSA where most people are diagnosed at
115 advanced stages and where access to treatment is limited⁵. HCV is responsible for an estimated 21% of
116 cancer deaths worldwide, corresponding to 167,000 deaths in 2015, including 8,000 and 31,000 deaths
117 in Central and West Africa, respectively⁶. In 2016, the World Health Organization (WHO) developed a
118 global health strategy to eliminate viral hepatitis with two main objectives to be reached by 2030:
119 reducing the number of new cases of viral hepatitis by 90%, and reducing viral hepatitis-related mortality
120 by 65%¹. Antiviral treatment using Direct Acting Antivirals (DAAs) is one of the core interventions
121 needed to reach these targets.

122 In 2014, the advent of second generation DAAs, which have a short treatment duration (8 to 16 weeks),
123 radically changed the hepatitis C landscape. DAAs are highly effective, with sustained virologic
124 response (SVR) rates estimated between 93% and 97% in trials conducted in high-income settings^{7–11}.
125 In addition, they are very well tolerated, making them easier to manage than interferon-based regimens.

126 The 2016 WHO guidelines recommending sofosbuvir/daclatasvir, sofosbuvir/ledipasvir or
127 sofosbuvir/ribavirin for the treatment of CHC in adults¹² were updated in 2018, with pangenotypic
128 DAAs regimens achieving SVR rates of over 85% across all seven major HCV genotypes¹³.

129 The short-term efficacy and tolerability of these regimens were recently reported in West and Central
130 Africa¹⁴ and in East Africa¹⁵. Despite their effectiveness and increasing low-cost availability in most
131 countries, DAAs remain inaccessible for the large majority of patients with CHC living in SSA, where
132 the treatment rate was estimated to be as low as 2% of diagnosed cases in 2015¹.

133 To provide further evidence of the benefits of introducing DAAs-based treatments into National
134 Hepatitis Programs in West and Central Africa, we used a modelling approach to assess the long-term
135 clinical outcomes of treating CHC patients with sofosbuvir-based regimens in Cameroon, Côte d'Ivoire
136 and Senegal. We discussed the affordability of these treatments in all three countries, by considering
137 government health expenditures (HE), private HE and patient willingness-to-pay.

138 **METHODS**

139 **Study design**

140 A Markov cohort model was developed to simulate lifetime CHC progression and to assess the long-
141 term clinical benefits of DAAs in terms of mortality and morbidity. With near-zero CHC treatment rates
142 in the study countries¹, we decided to use the status-quo (i.e. no HCV treatment, whether DAAs or
143 Interferon-based) as a comparator.

144

145 **Target population**

146 We simulated CHC progression, with and without treatment, in fictive cohorts of patients diagnosed
147 with CHC in Cameroon, Côte d'Ivoire and Senegal. Cohort sizes were estimated for each country using
148 the national population size, chronic HCV prevalence and diagnosis rates. Given that CHC is generally
149 diagnosed late in the study countries - usually after the initial appearance of symptoms - we assumed a
150 mean age of 50 years at model entry^{14,15}. Patients were infected with genotypes 1, 2, or 4 and had no
151 other viral coinfections, history of liver decompensation, or HCC. The proportion of women was 53%
152 in Senegal, 50% in Cameroon and 49% in Côte d'Ivoire, which corresponds to the demographic structure
153 of the population at 50 years of age in these countries¹⁶⁻¹⁸.

154

155 **Outcome measures**

156 We compared the following outcomes with and without treatment: mortality assessed using life-years
157 (LY), morbidity assessed using LY with compensated cirrhosis (CC), decompensated cirrhosis (DC)
158 and HCC as well as the evolution over time of the number (%) of patients in each disease stage.
159 Treatment benefits were assessed in life-years saved (LYS) and LY avoided in CC, DC and HCC stages.

160

161 **Model description**

162 The structure of the model is depicted in [Figure 1](#). Markov models with a similar structure have been
163 widely used in the literature for simulating CHC progression¹⁹.

164 The initial distribution of patients in the different health states defined according to the natural history
165 of CHC (including fibrosis stage measured with the METAVIR scoring system F0 to F3, CC, DC and
166 HCC) were as follows: 7.6% were in F0, 39.2% in F1, 26.2% in F2, 18.6% in F3 and 8.4% in CC²⁰. At
167 model entry, all patients had a detectable VL. Cycle durations were set to one year to reflect both the
168 relatively slow progression of the disease and data availability, except the first cycle whose duration
169 was set to 24 weeks (i.e., 12 weeks of treatment and 12 weeks of follow-up post-treatment). We assumed
170 that transitions between health states occurred in the middle of the cycles using half-cycle corrections²¹.

171 Disease progression over cycles depended on whether or not patients in the fictive cohorts received
172 sofosbuvir-based regimens and on whether or not they achieved SVR at the end of the treatment cycle.

173 In the cohorts without treatment, all patients with uncontrolled VL progressed to more advanced disease
174 stages according to the natural evolution of the infection.

175 In the cohorts with treatment, patients with mild fibrosis (F0, F1, F2, F3) or CC were all eligible for
176 treatment in accordance with 2016 WHO guidelines¹². At the end of the treatment cycle, patients in the
177 fictive cohorts either achieved SVR (cured) or did not (not cured). Although the first cycle duration
178 (corresponding to the treatment and follow-up post-treatment periods) was relatively short (i.e. 24
179 weeks), we assumed that the disease could progress to a more advanced stage for some patients during
180 that cycle. In the subsequent cycles, we assumed that apart from patients in the CC and DC health states
181 at the end of the treatment cycle, cured patients did not progress to a more advanced disease stage⁴. In
182 addition, as fibrosis improvements observed after treatment in cured patients cannot be attributed with
183 certainty to histological recovery, we made the conservative hypothesis that no fibrosis reversal occurred
184 in those patients^{22,23}. We also assumed that cured patients had a risk of reinfection in the subsequent
185 cycles but were not newly treated¹³. Reinfected or uncured patients had uncontrolled VL and therefore
186 progressed through the different disease stages as untreated patients.

187 In all cohorts, patients had a risk of non-CHC-related death in all health states, corresponding to the
188 “natural mortality” rate. Additionally, patients in the F3, CC, DC and HCC health states had a risk of
189 CHC-related death.

190

191 **Model inputs**

192 All parameters were derived from the literature by prioritizing data from SSA countries where available.
193 The HCV viremic prevalence and diagnostic rate were obtained from Chan et al. (2017)²⁴ for Cameroon,
194 and from the WHO 2017 report¹ for Senegal and Côte d’Ivoire.

195 DAAs treatment effectiveness was obtained from the ANRS 12311 TAC trial which included 120 CHC
196 patients treated either with sofosbuvir and ledipasvir (for genotypes 1 and 4) or with sofosbuvir and
197 ribavirin (for genotype 2)¹⁴. As SVR rates were not significantly different across genotypes, countries
198 or HIV co-infection status, we considered an overall 89.2% [95% Confidence Intervals (CI): 84.5; 93.8]
199 probability of treatment success in the model, irrespective of regimen, genotype, country or HIV co-
200 infection status.

201 In the absence of SSA country-specific data, transition probabilities between fibrosis stages without
202 treatment were obtained from a meta-analysis²⁵, while probabilities of transition from F3 to advanced
203 stages (CC, DC and HCC) were derived from Dienstag et al. (2011)²⁶. Transition probabilities
204 (irrespective of viremic status) from CC (to DC and to HCC) and from DC (to HCC) came from Nahon

205 et al. (2018)⁴ and Planas et al. (2004)²⁷, respectively. Annual probabilities of death associated with CC
206 and DC were obtained from Dienstag et al. (2011)²⁶ and Planas et al. (2004)²⁷, respectively.

207 As therapeutic options for patients with HCC living in the study countries were very limited, we
208 estimated the annual probability of death using HCC survival data for patients who did not receive
209 specific treatment for liver cancer in a multi-country observational study conducted in SSA²⁸.

210 All-cause mortality probabilities according to age and country were obtained from WHO mortality
211 tables²⁹. The probability of reinfection or relapse in patients achieving SVR after treatment was sourced
212 from a meta-analysis including studies conducted in mono-HCV infected patients living in high-income
213 countries (HIC) who had no specific risk factors for reinfection³⁰. All parameter values and their sources
214 are presented in [Table 1](#) (See also the Appendix 1 for further details).

215

216 **Internal consistency**

217 We tested the internal validity of our model i) by simulating a treated cohort with an SVR equal to zero
218 (all results should be identical for the treated and untreated cohorts); and ii) by assuming that the
219 probabilities of death associated with liver complications in F3, CC, DC and HCC stages were equal to
220 zero (life expectancy at 50 years is expected to be close to that of the general population of the same
221 age).

222

223 **Sensitivity analysis**

224 A probabilistic sensitivity analysis was conducted to assess parameter uncertainty in the model, in
225 accordance with international guidelines³¹. Model parameters were sampled from predefined
226 distributions over 1000 simulations (See the Appendix 1 for further details).

227 In addition, a deterministic sensitivity analysis was conducted to explore specific scenarios and to take
228 heterogeneity into account (i.e. specific subgroups). First, we simulated long-term clinical outcomes in
229 the fictive cohorts of HIV/HCV co-infected patients assuming they had a higher risk of HCV reinfection
230 than mono-infected patients³⁰. Second, we used a younger fictive cohort (35 years) to estimate the effect
231 of early diagnosis. In addition, cohorts with different initial disease stages were simulated to assess the
232 impact of initiating DAAs at different stages. Based on the TAC trial data¹⁴, we considered a lower SVR
233 rate (estimated at 78.6%) for patients at CC stage. Third, we simulated a scenario where patients were
234 treated using the most recent pangenotypic DAAs regimen, sofosbuvir/daclatasvir, recommended in the
235 2018 WHO guidelines¹³. As no data on SVR was available for this regimen in SSA, the SVR rate was
236 estimated at 90.8% using data from a French national cohort³² adjusted for a potential lower
237 effectiveness in SSA compared with HIC, as suggested by results from the TAC and SHARED trials^{14,15}.

238 Analyses were performed using R, version 3.6.0 (packages *markovchain*³³).

239 RESULTS

240 Internal consistency of the model

241 When we simulated a treated cohort with an SVR equal to zero, results for the two cohorts (treated and
242 untreated) were identical. In the second extreme value analysis, life expectancy at 50 years was
243 estimated at 22.6 years in Cameroon, 20.9 in Côte d'Ivoire and 24.2 in Senegal, which is in line with
244 WHO estimates on life expectancy in the general population of the same age²⁹.

245

246 Base-case analysis

247 At the current diagnostic rate^{1,24}, the number of patients diagnosed with CHC was estimated at 3,224 in
248 Cameroon, 9,748 in Côte d'Ivoire and 6,358 in Senegal. [Figure 2](#) illustrates the impact of sofosbuvir-
249 based treatment on liver-related mortality due to CHC over the lifetime of the cohorts in each study
250 country. Without treatment, the share of CHC-related mortality as part of global mortality was 36.5%,
251 33.2% and 39.5% in Cameroon, Côte d'Ivoire and Senegal, respectively, versus 9.8%, 9.1% and 10.5%
252 with treatment, respectively. Accordingly, 863, 2,350 and 1,843 deaths, respectively, could be avoided
253 with treatment, corresponding to a 73% reduction of liver-related mortality in the population diagnosed
254 with CHC.

255 [Table 2](#) shows, for each cohort in each country: i) life expectancy at 50 years (assessed using the mean
256 number of LY per patient in the cohorts with and without treatment) and LYS per patient with treatment,
257 ii) morbidity assessed using the mean number of LY per patient at the CC and DC stages with and
258 without treatment, and the mean number of LY avoided in the CC and DC stages per patient with
259 treatment. LYS [95% CI] with treatment were estimated at 3.3 [2.5; 5.7] per patient in Cameroon, 2.7
260 [2.1; 4.8] in Côte d'Ivoire and 3.6 [2.8; 6.3] in Senegal. In addition, the mean number of LY spent in the
261 most advanced stages in cohorts with treatment decreased by a factor of approximately 2, 3 and 10 in
262 the CC, DC and HCC stages, respectively, compared with patients not treated. We therefore estimated
263 that, on average, treatment resulted in between 1.3 to 1.6 LY avoided and 0.4 to 0.5 LY avoided per
264 patient in the CC and DC stages, respectively, depending on the country.

265 [Figure 3](#) illustrates the number (%) of patients with cirrhosis (CC and DC) over the cohorts' lifetime in
266 the study countries. Without treatment, the number of patients with CC and DC reached a maximum
267 approximately 11 and 15 years after CHC diagnosis, respectively. In the untreated cohorts,
268 approximately 15% of patients still alive in each of the study countries after 11 years had CC compared
269 with 6% in the treated cohorts. After 15 years, approximately 5% of patients still alive in the treated
270 cohorts had DC compared with 1% in the treated cohorts. The number of patients with CC reduced by
271 approximately 55% after 11 years and the number of patients with DC by approximately 75% after 15
272 years. Finally, after 20 years, the estimated proportion of patients with HCC represented 0.6%-0.7% of

273 patients still alive in the untreated cohorts versus 0.1% in the treated cohorts in the three countries. This
274 indicates a significant decrease of 87% (Supplementary [Table A1](#)).

275

276 **Sensitivity analysis**

277 Results from the deterministic sensitivity analysis are presented in supplementary [Tables A2 to A9](#) and
278 in supplementary [Figures 1 and 2](#), which show the mean [95% CI] number of LY avoided in CC and
279 DC stages per patient. For the fictive cohorts of HIV/HCV co-infected patients, mortality and morbidity
280 outcomes considerably improved with treatment but clinical benefits were smaller than in the base-case
281 due to higher reinfection rates in this population. LYS [95% CI] were only 2.6 [1.7;5.6] per patient in
282 Cameroon, 2.2 [1.3;4.9] in Côte d'Ivoire and 2.8 [1.8;6.0] in Senegal. Furthermore, patients spent 0.4 to
283 0.5 additional LY at the CC stage and 0.1 additional LY at the DC stage compared with the base-case
284 (Table A2).

285 Early diagnosis and treatment initiation (at 35 years) would save 5.9 to 7.9 additional LY compared with
286 the base-case. Depending on the country, 1.1 to 1.4 additional LY in the CC stage and 0.4 to 0.5
287 additional LY in the DC stage would be avoided compared with the base-case ([Table A3](#)).

288 When all the patients of the cohorts started treatment at F0, F1 or CC, treatment benefits were smaller
289 than in the base-case, for both mortality and morbidity ([Tables A4, A5 and A8](#)). Conversely, treatment
290 benefits were larger than in the base-case when we assumed that all patients started treatment at the F2
291 or F3 stage ([Tables A6-A7](#)). When all patients initiated treatment at the F3 stage, the LYS per patient
292 increased to 6.3 to 8.0 depending on the country, and LY avoided in the CC and DC states varied
293 between 3.2 to 3.6 years and 0.9 to 1 years, respectively.

294 Finally, when considering the most recent pangenotypic DAAs regimen (sofosbuvir/daclatasvir),
295 mortality and morbidity outcomes were quite similar to the base-case ([Table A9](#)).

296

297

298 **DISCUSSION**

299 This modelling study provides the first assessment of the long-term clinical benefits of DAAs treatment
300 in patients diagnosed with CHC living in West and Central Africa.

301 The number of people living with CHC is estimated at 88,358 in Cameroon, 165,776 in Côte d'Ivoire
302 and 108,134 in Senegal. At current diagnosis and treatment rates^{1,24}, an estimated 3,224, 9,748 and 6,358
303 people have been diagnosed, but only 0.12% to 0.31% of them benefit from treatment (including
304 interferon-based treatment)¹³.

305 Our findings showed that treating all patients currently diagnosed with CHC with DAAs in the three
306 study countries could dramatically decrease both CHC-related mortality and morbidity. We estimated
307 that DAAs would avoid 863, 2,350 and 1,843 deaths in Cameroon, Côte d’Ivoire and Senegal,
308 respectively, and save 2.7-3.6 LY per patient once diagnosed. Furthermore, as treatment stops disease
309 progression (except at the most advanced stages), the number of LY spent in the CC, DC and HCC
310 stages would decrease by approximately 2, 3 and 10 times, respectively, compared with the status-quo.
311 Sensitivity analysis also indicated that early diagnosis and treatment initiation dramatically improved
312 survival and reduced morbidity, compared with the base-case. Treatment benefits were the highest when
313 all patients started treatment at the F2 or F3 stage.

314

315 To date, DAAs short-term effectiveness in SSA has been assessed in only two pilot trials with a
316 relatively small number of patients in each (300 in Rwanda¹⁵ and 120 in Côte d’Ivoire, Cameroon and
317 Senegal¹⁴). Recently, modelling studies - all in high- or middle-income countries - also predicted the
318 impact of DAAs treatment on CHC-associated long-term disease burden and mortality. In a recent study
319 conducted in China, simulations for a cohort of 10,000 CHC patients over their lifetime, highlighted that
320 various DAAs regimens would reduce the incidence of CHC-related liver sequelae and mortality
321 significantly more than interferon/ribavirin-based regimens³⁴. Our findings are also consistent with those
322 of a study assessing the long-term effectiveness of different HCV treatment strategies in Egypt which
323 showed that immediate treatment of patients at stages F1 to F3 was more effective than delaying
324 treatment until more advanced stages³⁵.

325

326 **Public health policy recommendations**

327 In order for DAAs to have any impact in poor resource settings, a number of barriers need to be removed.
328 These are mainly linked to suboptimal HCV screening and to the high costs of DAAs.

329

330 ***Hepatitis C screening***

331 Scaling-up access to hepatitis C testing and earlier CHC diagnosis requires the availability of simplified
332 and low-cost diagnostic tools adapted to resource-limited settings. Current diagnosis relies on a two-
333 step procedure involving antibodies detection followed, if tests prove positive, by the quantification of
334 HCV ribonucleic acid using real-time quantitative polymerase chain reaction (PCR) assay. This
335 technique is costly (between 55 and 110 US\$/test) and requires trained lab technicians and equipment,
336 which is currently only available in a small number of reference laboratories in SSA. Furthermore, even
337 when PCR testing is available, the two-step procedure generates loss to follow-up because of the
338 additional time and large costs incurred by patients³⁶. Innovative means to both diagnose CHC cheaply

339 and quickly using a single test are needed³⁷. Existing alternatives include dried blood spot tests and
340 point-of-care and HCV core antigen measurements. The latter is an indirect marker of viral replication
341 with good performance already demonstrated in the SSA setting³⁸. In addition, a test-and-treat public
342 health approach should be favoured, as recommended by the 2018 WHO guidelines¹³, in order to ensure
343 that patients with a positive diagnosis are promptly treated.

344

345 *Diagnosis and treatment costs*

346 Although dramatic decreases in DAAs prices have been obtained in low-income countries (LIC)
347 following Gilead's DAAs tiered pricing policy and the entry of generics³⁹, the diagnosis and treatment
348 of CHC is still very expensive⁴⁰. A 12-week sofosbuvir/ledipasvir regimen manufactured by Gilead costs
349 approximately US\$1150 in the study countries, while generic drugs could become available for only
350 US\$140 according to the 2017 Médecins Sans Frontières report⁴¹. Data on costs collected in the TAC
351 trial in the same countries showed that the global cost for treating patients with DAAs (including
352 examinations and consultations) ranges from US\$1503 per patient in Côte d'Ivoire to US\$1692 in
353 Cameroon⁴². Treating all patients currently diagnosed with CHC in the three study countries with DAAs
354 would therefore imply a total cost of approximately US\$5.4 million in Cameroon, US\$14.6 million in
355 Côte d'Ivoire and US\$10.3 million in Senegal. Furthermore, if the WHO target of treating 80% of CHC
356 patients is to be reached, the costs involved will be much higher (US\$140 million in Cameroon, US\$199
357 million in Côte d'Ivoire and US\$119 million in Senegal). The fundamental issue is whether countries
358 and patients could afford to pay these costs.

359 In our study countries, health systems are mainly funded by private HE through out-of-pocket payments
360 (OOP) which represent 70%, 40% and 51% of the total HE in Cameroon, Côte d'Ivoire and Senegal⁴³,
361 respectively. Total current HE is estimated at US\$1500 million in Cameroon, US\$1611 million in Côte
362 d'Ivoire and US\$816 million in Senegal, with the government's share estimated at US\$195, US\$419
363 and US\$269 million, respectively.

364 According to current patterns for financing health in the study countries, patients would incur direct
365 OOP for CHC treatment costs of US\$1185 in Cameroon, US\$601 in Côte d'Ivoire and US\$828 in
366 Senegal. Considering that the per capita gross domestic product (GDP) is US\$1374, US\$1534 and
367 US\$1269 in the respective countries, privately paying for health treatment is clearly impossible for most
368 patients.

369 Data from the TAC trial also indicated that over 75% of patients were willing to pay for diagnosis,
370 treatment and/or care (See Appendix 2). However, when probed further about the amount they were
371 willing to pay, the median ranged from US\$126 in Côte d'Ivoire to US\$220 in Cameroon. Such amounts
372 would cover only 8 to 13% of the costs of CHC treatment in the three study countries.

373 If governments were to bear the total costs of CHC treatment alone, treating all patients diagnosed with
374 CHC in the three countries would imply a relatively low increase in current government HE (i.e., from
375 2.8% in Cameroon to 3.8% in Senegal). However, if the WHO target of treating 80% of the patients
376 living with CHC is to be reached, the additional resources required will be much greater, specifically
377 1.5 to 1.6 times current government HE in the studied countries.

378 These data suggest that the WHO target cannot be met in these countries without i) a large decrease in
379 DAAs prices through the development of the production and wider use of generics ii) political
380 commitment and increased national HE to meet the target of at least 15% of GDP as set out in the Abuja
381 declaration⁴⁴, iii) global health financing mechanisms, including the integration of hepatitis C epidemic
382 control strategies within organisations tackling HIV, such as the Global Fund to Fight AIDS,
383 Tuberculosis and Malaria.

384

385 **Study limitations**

386 Our study has limitations. First, a number of model parameters are not specific to SSA. This is especially
387 true for transition probabilities, which were obtained from studies conducted in HIC. In SSA, where
388 access to specialized care for liver complications is limited, disease progression and mortality may occur
389 faster. This may have resulted in an underestimation of mortality in the absence of treatment and
390 consequently, an underestimation of DAAs benefits. Furthermore, to estimate the risk of reinfection, we
391 used data from a meta-analysis including studies conducted in mono-HCV infected patients living in
392 HIC without specific risk factors for reinfection³⁰. This could have resulted in an overestimation of
393 treatment benefits, as patients living in SSA may have a higher risk of reinfection than mono-infected
394 patients in HIC, due to a higher risk of iatrogenic infections. To address uncertainty in the model's
395 parameters, a probabilistic sensitivity analysis was conducted in line with international standards³¹.

396 Second, we extrapolated long-term clinical outcomes using a Markov cohort model which does not
397 account for HCV transmission. Although we acknowledge that dynamic models may be more
398 appropriate to assess the full health impact of DAAs, including HCV transmission reduction⁴⁵, we chose
399 to focus on the estimation of clinical outcomes using a Markov model, which requires fewer hypotheses
400 and fewer data and is faster to implement. In addition, a limitation of this approach is its inability to
401 simulate patient trajectories using specific individual risk factors that may affect disease progression
402 over time. Despite this, Markov models have been widely used in the literature for simulating CHC
403 progression and treatment effectiveness⁴⁶.

404

405 **Conclusion**

406 Our study provides important information for health policy recommendations on the long-term clinical
407 benefits of DAAs in West and Central Africa and constitutes a first step towards a full-scale analysis for
408 SSA. Our findings strongly argue for rapid scale-up of DAAs treatment in this region, and highlight the
409 need for financial and political commitment and support, from both national governments and
410 international institutions.

411

412 **Authors' contributions:**

413 Study concept and design: S.B., M.E.W. and K.L.; data acquisition: M.B., M.E.W. C.K., R.M., M.S.,
414 and A.A.; data analysis and interpretation: S.B., M.B., M.L.N., M.E.W., M.L., K.L.; drafting of the
415 manuscript: SB; critical revision of the manuscript for important intellectual content: S.B., M.B.,M.L.N.,
416 M.E.W., M.L., B.S., C.K., R.M., M.S., N.R., A.A. K.L.; statistical analysis: M.B. and M.L.N.; obtained
417 funding: SB; administrative, technical, and material support: M.L., B.S., R.M., N.R., A.A. and K.L;
418 study supervision: SB. The corresponding author had full access to all the data in the study and had final
419 responsibility for the decision to submit for publication.

420

421

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Tables

Table 1: Model parameters

Model parameter(s)	Base-case value	Distribution	95% Confidence Intervals	Source	Further description
Cohort characteristics					
Start age of cohort (years)	50	–	–	14,15	35 years – age considered in scenario analyses
Proportion of women at 50 years		–	–		
<i>Cameroon</i>	0.489			17	
<i>Côte d'Ivoire</i>	0.499			18	
<i>Senegal</i>	0.531			16	
Fibrosis Initial Stages at treatment initiation					
F0	0.076	–		20	Scenario analyses considered alternative distributions where all CHC patients start treatment: i) in F0, ii) in F1, iii) in F2, iii) in F3, iv) in CC.
F1	0.392				
F2	0.262				
F3	0.186				
CC	0.084				
DAAs effectiveness					
SVR12 SOF/RBV or SOF/LDV	0.892	–	[0.845;0.938]	TAC trial ¹⁴	
SVR12 SOF/DCV	0.908	–	[0.860;0.955]	HEPATHER cohort ³²	
SVR12 SOF/RBV or SOF/LDV in cirrhotic patients	0.786	–	[0.524; 0.924]	TAC trial ¹⁴	
Natural history of CHC (in untreated or uncured patients): annual disease transition probabilities					
All stages → non-CHC related mortality	–	–	–	29	Country, sex and age-specific
F0 → F1	0.079	Beta(21.1;234.7)	[0.052;0.119]	25	
F1 → F2	0.059	Beta(88.4;1399.1)	[0.048;0.072]	25	
F2 → F3	0.108	Beta(30.0;238.6)	[0.077;0.152]	25	
F3 → CC	0.077	Beta(14.8;164.1)	[0.047;0.127]	25	
F3 → DC	0.012	Beta(7.0;558.0)	[0.005;0.023] [†]	26	
F3 → HCC	0.011	Beta(7.0;558.0)	[0.005;0.023] [†]	26	
F3 → CHC related mortality	0.008	Beta(0.4;18.7)	[0.003;0.019] [†]	26	
CC → DC	0.041	Beta(99.5;2290.4)	[0.034;0.050] [†]	4	
CC → HCC	0.042	Beta(90.0;2048.7)	[0.034;0.051] [†]	4	
CC → CHC related mortality	0.026	Beta(11.5;407.0)	[0.014;0.045] [†]	26	
DC → HCC	0.068	Beta(37.9;514.7)	[0.049;0.091] [†]	27	
DC → CHC related mortality	0.130	Beta(75.7;489.9)	[0.107;0.163] [†]	27	
HCC → CHC related mortality	0.900	Beta(186.3;19.9)	[0.86;0.94] [†]	28	

Table 1 (continued)					
Model parameter(s)	Base-case value	Distribution	95% Confidence Intervals	Source	Further description
CHC progression after DAAs (in cured patients): annual disease transitions probabilities					
CC → DC	0.023	Beta(14.1;540.5)	[0.014;0.040] [†]	4	
CC → HCC	0.014	Beta(37.9;514.7)	[0.007;0.029]	4	
CC → CHC related mortality	0.026	Beta(11.5;407.0)	[0.014;0.045] [†]	26	
DC → HCC	0.068	Beta(37.9;514.7)	[0.049;0.091] [†]	27	
DC → CHC related mortality	0.130	Beta(75.7;489.9)	[0.107;0.163] [†]	27	
HCC → CHC related mortality	0.900	Beta(186.3;19.9)	[0.86;0.94]	28	
Annual probabilities of reinfection					
- <i>mono-infected</i>	0.002	Beta(13.2;7051.8)	[0.001;0.003]	30	
- <i>HIV co-infected</i>	0.032	Beta(0.2;13.1)	[0.000;0.123]	30	
Epidemiology					
Total population, aged 18-100 (2018)					
<i>Senegal</i>	8318000			47	Population age structure is divided into 5-year classes
<i>Côte d'Ivoire</i>	12752000				
<i>Cameroon</i>	12622600				
Viremic prevalence					
<i>Senegal</i>	1.3%		[1.1%-1.4%]	2	
<i>Côte d'Ivoire</i>	1.3%		[1.1%-1.4%]		
<i>Cameroon</i>	0.7%		[0.5%-0.8%]		
% diagnosed with CHC					
<i>Senegal</i>	6.0%			1	Number of people diagnosed with CHC / number of viremic cases
<i>Côte d'Ivoire</i>	6.0%				
<i>Cameroon</i>	4.0%			24	
% diagnosed with CHC and treated					
<i>Senegal</i>	2.0%			1	Annual number of treated CHC patients / total number of diagnosed cases
<i>Côte d'Ivoire</i>	2.0%				
<i>Cameroon</i>	7.9%			24	
Number of patients eligible for treatment					
<i>Senegal</i>	6358				Total population * viremic prevalence * % diagnosed * (1-% treated)
<i>Côte d'Ivoire</i>	9748				
<i>Cameroon</i>	3224				

[†] 95% Confidence Intervals calculated using the Wilson score formula.

Abbreviations: CHC, Chronic Hepatitis C infection; F0, F1, F2, F3, METAVIR fibrosis stages; CC, Compensated Cirrhosis; DC, Decompensated Cirrhosis; DAAs, Direct Action Antivirals; SVR12, Sustained virologic response 12 weeks after the end of treatment.

Table 2: Mortality and morbidity in fictive cohorts of CHC patients with and without DAAs treatment (n=3224 in Cameroon, n=9748 in Côte d'Ivoire, n=6358 in Senegal)

	Cameroon		Côte d'Ivoire		Senegal	
	With treatment	Without treatment	With treatment	Without treatment	With treatment	Without treatment
Life expectancy at 50 years and life years saved per patient with treatment						
Mean [95% Confidence Intervals] life-years per patient	21.2 [20.6;21.4]	18 [14.9;18.8]	19.7 [19;19.8]	16.9 [14.3;17.5]	22.7 [21.8;22.9]	19.1 [15.7;19.9]
Mean [95% Confidence Intervals] life-years saved (LYS) per patient [†]	3.3 [2.5;5.7]		2.7 [2.1;4.8]		3.6 [2.8;6.3]	
Life years spent in CC (DC) and life years avoided in the CC (DC) stages per patient with treatment						
Mean [95% Confidence Intervals] life-years spent in CC per patient	1.2 [1;1.4]	2.7 [1.6;3.3]	1.2 [0.9;1.3]	2.4 [1.5;3.1]	1.3 [1;1.5]	2.9 [1.7;3.7]
Mean [95% Confidence Intervals] life-years in CC stage avoided per patient [‡]	1.4 [0.6;2.0]		1.3 [0.5;1.8]		1.6 [0.6;2.3]	
Mean [95% Confidence Intervals] life-years spent in DC per patient	0.2 [0.1;0.2]	0.7 [0.4;0.9]	0.2 [0.1;0.2]	0.6 [0.4;0.8]	0.2 [0.1;0.3]	0.7 [0.4;0.9]
Mean [95% Confidence Intervals] life-years in DC stage avoided per patient [‡]	0.5 [0.3;0.7]		0.4 [0.2;0.6]		0.5 [0.3;0.7]	

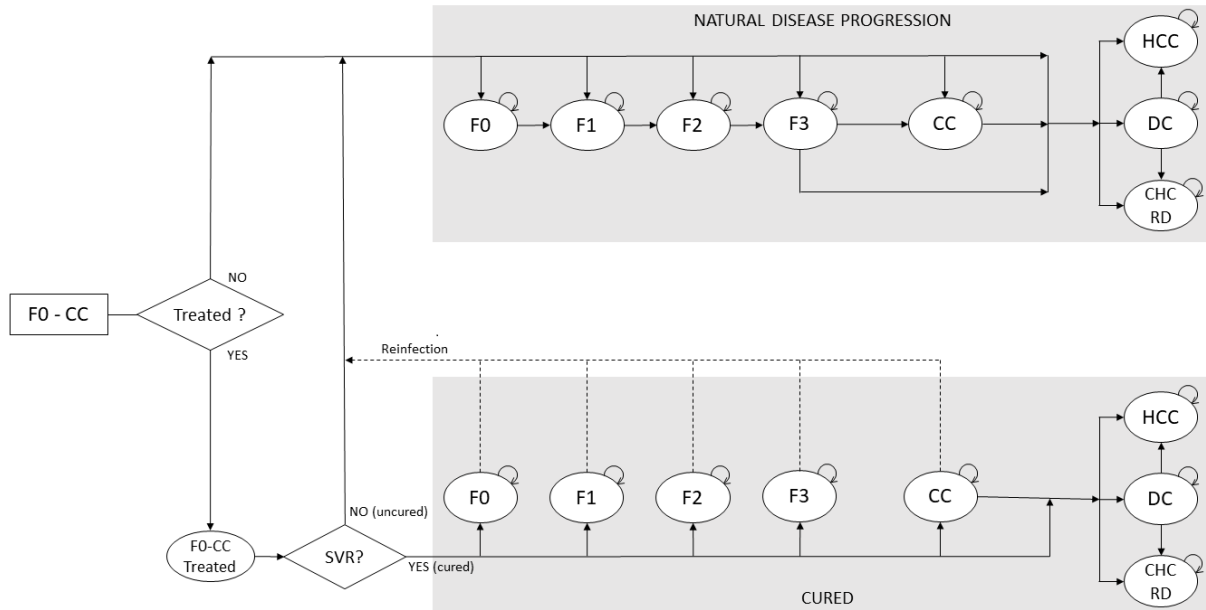
[†] Life-years saved per patient are calculated as the number of life-years per patient with treatment minus the number of life-years per patient without treatment.

[‡] Life-years avoided in the CC (DC) stages per patient are calculated as the number of life-years per patient spent in the CC (DC) stage without treatment minus the number of life-years per patient spent in the CC (DC) stage with treatment.

Abbreviations: CHC, Chronic Hepatitis C infection; DAAs, Direct Acting Antivirals; CC, Compensated Cirrhosis; DC, Decompensated Cirrhosis.

Figures

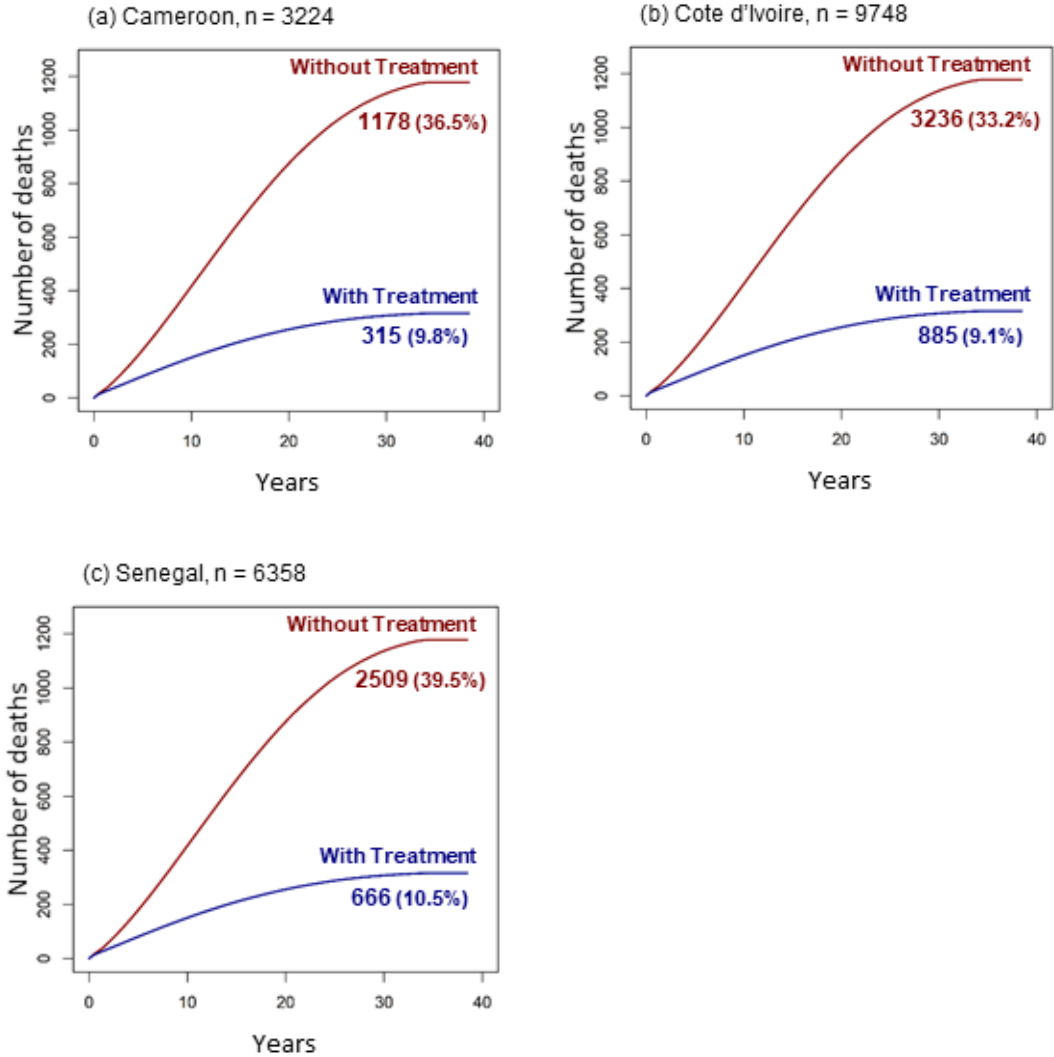
Figure 1: Diagram of the Markov cohort model



Legend: The ovals boxes represent the different health states of the model including fibrosis stage measured by the METAVIR scoring system (F0, F1, F2, F3), CC, DC, HCC and CHC RD. At model entry, all patients have a detectable viral load and are at the F0, F1, F2, F3 or CC stages. The two diamonds represent, respectively, whether patients received treatment (“yes” or “no”) and whether they achieved SVR after treatment or not (if “yes”, they are cured; if “not” they are uncured). Arrows on full lines denote the transitions between health states according to treatment decision and treatment success. Arrows on dashed lines show reinfection in cured patients. The upper part of the diagram, labelled “NATURAL DISEASE PROGRESSION”, describes the progression for patients with uncontrolled viral load (i.e. in absence of treatment, in case of treatment failure or reinfection). The lower part of the diagram, labelled “CURED”, describes the treatment benefits in cured patients (i.e., the disease progression stops except in patients in the CC or DC health state stage at the end of the treatment cycle). In all cohorts, patients had a risk of HCV-related death in all health states, corresponding to the “natural mortality” rate, which depends on age, gender and country. Additionally, patients who were in the F3, CC, DC and HCC health states had a risk of CHC-related death.

CHC, Chronic Hepatitis C; F0-F3, METAVIR fibrosis stages F0 to F3; CC, Compensated Cirrhosis; DC, Decompensated Cirrhosis; HCC, Hepatocellular Carcinoma; CHC RD, Chronic hepatitis C-related death; SVR: Sustainable Virologic Response.

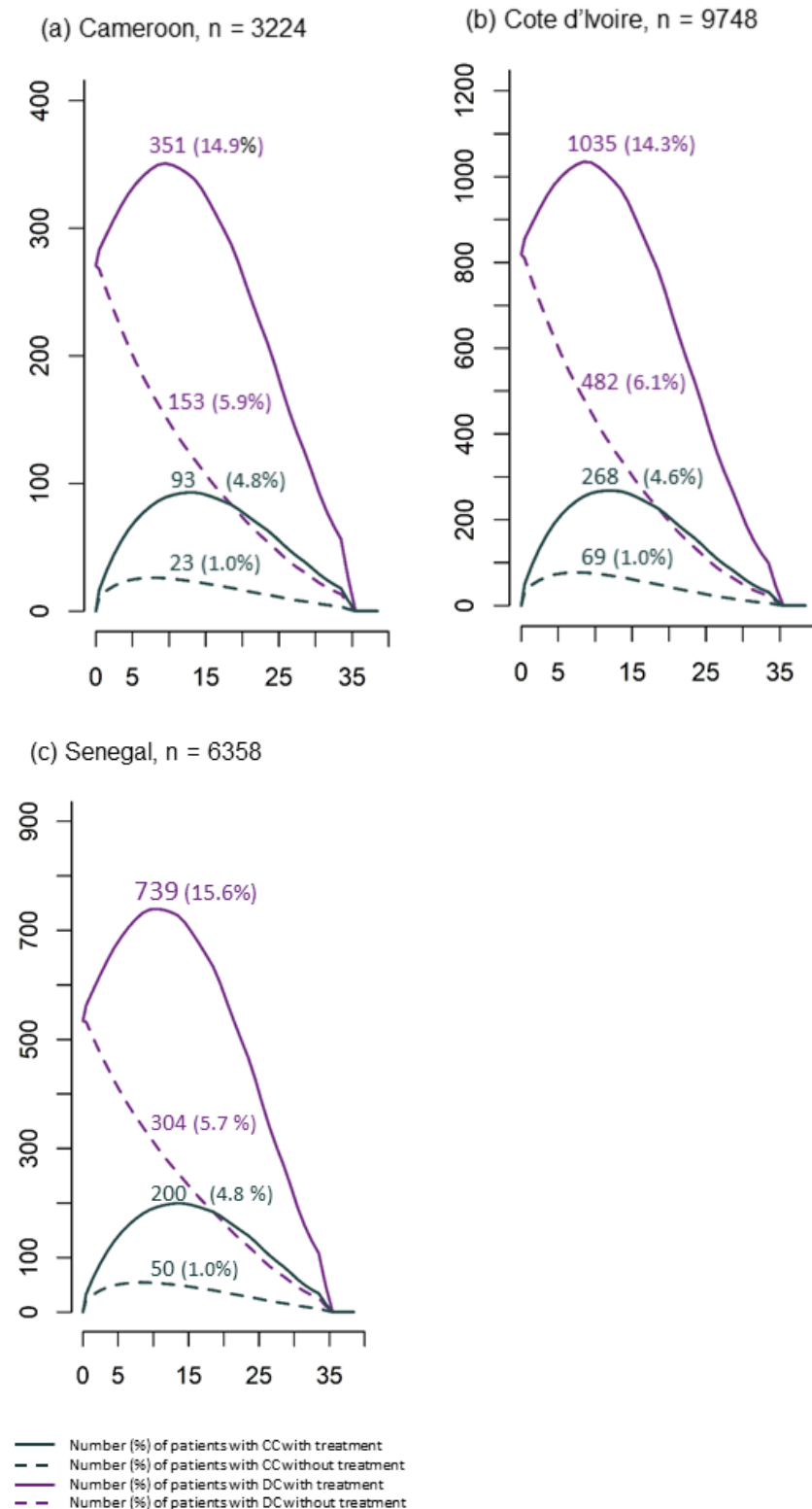
Figure 2: Liver disease-related deaths over lifetime with and without treatment in mono-infected patients diagnosed with chronic hepatitis C in Cameroon (Fig. 2a), Côte d’Ivoire (Fig. 2b) and Senegal (Fig. 2c)



Legend: The numbers (%) above each curve indicate, respectively: i) the number of liver disease-related deaths due to CHC over the cohorts’ lifetime with and without treatment; ii) the share of liver disease-related mortality due to CHC within global mortality with and without treatment.

CHC, Chronic Hepatitis C.

Figure 3 : Evolution over lifetime of the number (% among patients still alive) of patients with compensated cirrhosis and with decompensated cirrhosis in mono-infected patients diagnosed with chronic hepatitis C in Cameroon (Fig. 3a), Côte d'Ivoire (Fig. 3b) and Senegal (Fig. 3c)



Legend: The numbers (%) above each curve indicate, respectively: i) the number (%) of patients with CC 11 years after the diagnosis (with and without treatment), ii) the number (%) of patients with DC 15 years after the diagnosis (with and without treatment). The time-points of 11 and 15 years were chosen as they correspond to the approximate maximum number of patients with CC and DC, respectively (in the cohorts without treatment). CC, *Compensated Cirrhosis*; DC, *Decompensated Cirrhosis*.