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

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Ethics approval statement

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

Patient consent statement

Not applicable.

Permission to reproduce material from other sources

Not applicable.

ABSTRACT (word count: 249)

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

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

Results: Sofosbuvir-based treatment would save [mean, 95% Confidence Intervals] 3.3 (2.5;5.7) LY 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, approximately 6% (1%) of the patients still alive in each of the study countries would be in the CC (DC) health state 11 (15) years after CHC diagnosis, versus 15% (5%) without treatment. Scenario analysis showed earlier diagnosis and treatment initiation would dramatically improve LYS and morbidity.

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

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

Lay summary

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

INTRODUCTION

Viral hepatitis is a global public health issue affecting 325 million people in 2015, including 71 million with the hepatitis C virus (HCV)[1]. The burden of HCV infection is especially high in Sub-Saharan Africa (SSA), which accounts for 14% of the total number of people infected with HCV worldwide[2]. HCV viremic prevalence is unevenly distributed in this region, with the highest prevalence rates in Central (2.1%) and West (1.3%) Africa[2].

HCV causes both acute and chronic infection. While acute infection is usually asymptomatic and resolved spontaneously without treatment in 15-45% of infected persons, 60–80% of those infected develop chronic hepatitis C (CHC)[3]. In the absence of timely diagnosis and adequate treatment, CHC may progress to liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC)[4]. In addition, the risk of mortality associated with liver disease is high, especially in SSA where most people are diagnosed at advanced stages and where access to treatment is limited[5]. HCV is responsible for an estimated 21% of cancer deaths worldwide, corresponding to 167,000 deaths in 2015, including 8,000 and 31,000 deaths in Central and West Africa, respectively[6]. In 2016, the World Health Organization (WHO) developed a global health strategy to eliminate viral hepatitis with two main objectives to be reached by 2030: reducing the number of new cases of viral hepatitis by 90%, and reducing viral hepatitis-related mortality by 65%[1]. Antiviral treatment using Direct Acting Antivirals (DAAs) is one of the core interventions needed to reach these targets.

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

The 2016 WHO guidelines recommending sofosbuvir/daclatasvir, sofosbuvir/ledipasvir or sofosbuvir/ribavirin for the treatment of CHC in adults[12] were updated in 2018, with pangenotypic DAAs regimens achieving SVR rates of over 85% across all seven major HCV genotypes[13].

The short-term efficacy and tolerability of these regimens were recently reported in West and Central Africa[14] and in East Africa[15]. Despite their effectiveness and increasing low-cost availability in most countries, DAAs remain inaccessible for the large majority of patients with CHC living in SSA, where the treatment rate was estimated to be as low as 2% of diagnosed cases in 2015[1].

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

METHODS

Study design

A Markov cohort model was developed to simulate lifetime CHC progression and to assess the long-term clinical benefits of DAAs in terms of mortality and morbidity. With near-zero CHC treatment rates in the study countries[1], we decided to use the status-quo (i.e. no HCV treatment, whether DAAs or Interferon-based) as a comparator.

Target population

We simulated CHC progression, with and without treatment, in fictive cohorts of patients diagnosed with CHC in Cameroon, Côte d'Ivoire and Senegal. Cohort sizes were estimated for each country using the national population size, chronic HCV prevalence and diagnosis rates. Given that CHC is generally diagnosed late in the study countries - usually after the initial appearance of symptoms - we assumed a mean age of 50 years at model entry[14,15]. Patients were infected with genotypes 1, 2, or 4 and had no other viral coinfections, history of liver decompensation, or HCC. The proportion of women was 53% in Senegal, 50% in Cameroon and 49% in Côte d'Ivoire, which corresponds to the demographic structure of the population at 50 years of age in these countries[16–18].

Outcome measures

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

Model description

The structure of the model is depicted in Figure 1. Markov models with a similar structure have been widely used in the literature for simulating CHC progression[19].

The initial distribution of patients in the different health states defined according to the natural history of CHC (including fibrosis stage measured with the METAVIR scoring system F0 to F3, CC, DC and 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 CC[20]. At model entry, all patients had a detectable VL. Cycle durations were set to one year to reflect both the relatively slow progression of the disease and data availability, except the first cycle whose duration was set to 24 weeks (i.e., 12 weeks of treatment and 12 weeks of follow-up post-treatment). We assumed that transitions between health states occurred in the middle of the cycles using half-cycle corrections[21].

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

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

In the cohorts with treatment, patients with mild fibrosis (F0, F1, F2, F3) or CC were all eligible for treatment in accordance with 2016 WHO guidelines[12]. At the end of the treatment cycle, patients in the fictive cohorts either achieved SVR (cured) or did not (not cured). Although the first cycle duration (corresponding to the treatment and follow-up post-treatment periods) was relatively short (i.e. 24 weeks), we assumed that the disease could progress to a more advanced stage for some patients during that cycle. In the subsequent cycles, we assumed that apart from patients in the CC and DC health states at the end of the treatment cycle, cured patients did not progress to a more advanced disease stage[4]. In addition, as fibrosis improvements observed after treatment in cured patients cannot be attributed with certainty to histological recovery, we made the conservative hypothesis that no fibrosis reversal occurred in those patients[22,23]. We also assumed that cured patients had a risk of reinfection in the subsequent cycles but were not newly treated [13]. Reinfected or uncured patients had uncontrolled VL and therefore progressed through the different disease stages as untreated patients.

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

Model inputs

All parameters were derived from the literature by prioritizing data from SSA countries where available. The HCV viremic prevalence and diagnostic rate were obtained from Chan et al. (2017)[24] for Cameroon, and from the WHO 2017 report[1] for Senegal and Côte d'Ivoire.

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

In the absence of SSA country-specific data, transition probabilities between fibrosis stages without treatment were obtained from a meta-analysis[25], while probabilities of transition from F3 to advanced stages (CC, DC and HCC) were derived from Dienstag et al. (2011)[26]. Transition probabilities (irrespective of viremic status) from CC (to DC and to HCC) and from DC (to HCC) came from Nahon

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

As therapeutic options for patients with HCC living in the study countries were very limited, we estimated the annual probability of death using HCC survival data for patients who did not receive specific treatment for liver cancer in a multi-country observational study conducted in SSA[28].

All-cause mortality probabilities according to age and country were obtained from WHO mortality tables[29]. The probability of reinfection or relapse in patients achieving SVR after treatment was sourced from a meta-analysis including studies conducted in mono-HCV infected patients living in high-income countries (HIC) who had no specific risk factors for reinfection[30]. All parameter values and their sources are presented in Table 1 (See also the Appendix 1 for further details).

Internal consistency

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

Sensitivity analysis

A probabilistic sensitivity analysis was conducted to assess parameter uncertainty in the model, in accordance with international guidelines[31]. Model parameters were sampled from predefined distributions over 1000 simulations (See the Appendix 1 for further details).

In addition, a deterministic sensitivity analysis was conducted to explore specific scenarios and to take heterogeneity into account (i.e. specific subgroups). First, we simulated long-term clinical outcomes in the fictive cohorts of HIV/HCV co-infected patients assuming they had a higher risk of HCV reinfection than mono-infected patients[30]. Second, we used a younger fictive cohort (35 years) to estimate the effect of early diagnosis. In addition, cohorts with different initial disease stages were simulated to assess the impact of initiating DAAs at different stages. Based on the TAC trial data[14], we considered a lower SVR rate (estimated at 78.6%) for patients at CC stage. Third, we simulated a scenario where patients were treated using the most recent pangenotypic DAAs regimen, sofosbuvir/daclatasvir, recommended in the 2018 WHO guidelines[13]. As no data on SVR was available for this regimen in SSA, the SVR rate was estimated at 90.8% using data from a French national cohort[32] adjusted for a potential lower effectiveness in SSA compared with HIC, as suggested by results from the TAC and SHARED trials[14,15].

Analyses were performed using R, version 3.6.0 (packages m*arkovchain*[33]*).*

RESULTS

Internal consistency of the model

When we simulated a treated cohort with an SVR equal to zero, results for the two cohorts (treated and untreated) were identical. In the second extreme value analysis, life expectancy at 50 years was estimated at 22.6 years in Cameroon, 20.9 in Côte d'Ivoire and 24.2 in Senegal, which is in line with WHO estimates on life expectancy in the general population of the same age[29].

Base-case analysis

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

Table 2 shows, for each cohort in each country: i) life expectancy at 50 years (assessed using the mean number of LY per patient in the cohorts with and without treatment) and LYS per patient with treatment, ii) morbidity assessed using the mean number of LY per patient at the CC and DC stages with and without treatment, and the mean number of LY avoided in the CC and DC stages per patient with treatment. LYS [95% CI] with treatment were estimated at 3.3 [2.5; 5.7] per patient in Cameroon, 2.7 [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 most advanced stages in cohorts with treatment decreased by a factor of approximately 2, 3 and 10 in the CC, DC and HCC stages, respectively, compared with patients not treated. We therefore estimated that, on average, treatment resulted in between 1.3 to 1.6 LY avoided and 0.4 to 0.5 LY avoided per patient in the CC and DC stages, respectively, depending on the country.

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

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

Sensitivity analysis

Results from the deterministic sensitivity analysis are presented in supplementary Tables A2 to A9 and in supplementary Figures 1 and 2, which show the mean [95% CI] number of LY avoided in CC and DC stages per patient. For the fictive cohorts of HIV/HCV co-infected patients, mortality and morbidity outcomes considerably improved with treatment but clinical benefits were smaller than in the base-case due to higher reinfection rates in this population. LYS [95% CI] were only 2.6 [1.7;5.6] per patient in 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 0.5 additional LY at the CC stage and 0.1 additional LY at the DC stage compared with the base-case (Table A2).

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

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

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

DISCUSSION

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

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

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

To date, DAAs short-term effectiveness in SSA has been assessed in only two pilot trials with a relatively small number of patients in each (300 in Rwanda[15] and 120 in Côte d'Ivoire, Cameroon and Senegal[14]). Recently, modelling studies - all in high- or middle-income countries - also predicted the impact of DAAs treatment on CHC-associated long-term disease burden and mortality. In a recent study conducted in China, simulations for a cohort of 10,000 CHC patients over their lifetime, highlighted that various DAAs regimens would reduce the incidence of CHC-related liver sequelae and mortality significantly more than interferon/ribavirin-based regimens[34]. Our findings are also consistent with those of a study assessing the long-term effectiveness of different HCV treatment strategies in Egypt which showed that immediate treatment of patients at stages F1 to F3 was more effective than delaying treatment until more advanced stages[35].

Public health policy recommendations

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

Hepatitis C screening

Scaling-up access to hepatitis C testing and earlier CHC diagnosis requires the availability of simplified and low-cost diagnostic tools adapted to resource-limited settings. Current diagnosis relies on a two-step procedure involving antibodies detection followed, if tests prove positive, by the quantification of HCV ribonucleic acid using real-time quantitative polymerase chain reaction (PCR) assay. This technique is costly (between 55 and 110 US$/test) and requires trained lab technicians and equipment, which is currently only available in a small number of reference laboratories in SSA. Furthermore, even when PCR testing is available, the two-step procedure generates loss to follow-up because of the additional time and large costs incurred by patients[36]. Innovative means to both diagnose CHC cheaply

and quickly using a single test are needed[37]. Existing alternatives include dried blood spot tests and point-of-care and HCV core antigen measurements. The latter is an indirect marker of viral replication with good performance already demonstrated in the SSA setting[38]. In addition, a test-and-treat public health approach should be favoured, as recommended by the 2018 WHO guidelines[13], in order to ensure that patients with a positive diagnosis are promptly treated.

Diagnosis and treatment costs

Although dramatic decreases in DAAs prices have been obtained in low-income countries (LIC) following Gilead's DAAs tiered pricing policy and the entry of generics[39], the diagnosis and treatment of CHC is still very expensive[40]. A 12-week sofosbuvir/ledipasvir regimen manufactured by Gilead costs approximately US$1150 in the study countries, while generic drugs could become available for only US$140 according to the 2017 Médecins Sans Frontières report[41]. Data on costs collected in the TAC trial in the same countries showed that the global cost for treating patients with DAAs (including examinations and consultations) ranges from US$1503 per patient in Côte d'Ivoire to US$1692 in Cameroon[42]. Treating all patients currently diagnosed with CHC in the three study countries with DAAs would therefore imply a total cost of approximately US$5.4 million in Cameroon, US$14.6 million in Côte d'Ivoire and US$10.3 million in Senegal. Furthermore, if the WHO target of treating 80% of CHC patients is to be reached, the costs involved will be much higher (US$140 million in Cameroon, US$199 million in Côte d'Ivoire and US$119 million in Senegal). The fundamental issue is whether countries and patients could afford to pay these costs.

In our study countries, health systems are mainly funded by private HE through out-of-pocket payments (OOP) which represent 70%, 40% and 51% of the total HE in Cameroon, Côte d'Ivoire and Senegal[43], respectively. Total current HE is estimated at US$1500 million in Cameroon, US$1611 million in Côte d'Ivoire and US$816 million in Senegal, with the government's share estimated at US$195, US$419 and US$269 million, respectively.

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

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

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

These data suggest that the WHO target cannot be met in these countries without i) a large decrease in DAAs prices through the development of the production and wider use of generics ii) political commitment and increased national HE to meet the target of at least 15% of GDP as set out in the Abuja declaration[44], iii) global health financing mechanisms, including the integration of hepatitis C epidemic control strategies within organisations tackling HIV, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria.

Study limitations

Our study has limitations. First, a number of model parameters are not specific to SSA. This is especially true for transition probabilities, which were obtained from studies conducted in HIC. In SSA, where access to specialized care for liver complications is limited, disease progression and mortality may occur faster. This may have resulted in an underestimation of mortality in the absence of treatment and consequently, an underestimation of DAAs benefits. Furthermore, to estimate the risk of reinfection, we used data from a meta-analysis including studies conducted in mono-HCV infected patients living in HIC without specific risk factors for reinfection[30]. This could have resulted in an overestimation of treatment benefits, as patients living in SSA may have a higher risk of reinfection than mono-infected patients in HIC, due to a higher risk of iatrogenic infections. To address uncertainty in the model's parameters, a probabilistic sensitivity analysis was conducted in line with international standards[31].

Second, we extrapolated long-term clinical outcomes using a Markov cohort model which does not account for HCV transmission. Although we acknowledge that dynamic models may be more appropriate to assess the full health impact of DAAs, including HCV transmission reduction[45], we chose to focus on the estimation of clinical outcomes using a Markov model, which requires fewer hypotheses and fewer data and is faster to implement. In addition, a limitation of this approach is its inability to simulate patient trajectories using specific individual risk factors that may affect disease progression over time. Despite this, Markov models have been widely used in the literature for simulating CHC progression and treatment effectiveness[46].

Conclusion

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

Authors' contributions:

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., and A.A.; data analysis and interpretation: S.B., M.B., M.L.N., M.E.W., M.L., K.L.; drafting of the manuscript: SB; critical revision of the manuscript for important intellectual content: S.B., M.B.,M.L.N., 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 funding: SB; administrative, technical, and material support: M.L., B.S., R.M., N.R., A.A. and K.L; study supervision: SB. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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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		_	_		
Cameroon	0.489			[17]	
Côte d'Ivoire	0.499			[18]	
Senegal	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					
- *mono-infected*	0.002	Beta(13.2;7051.8)	[0.001;0.003]	[30]	
- *HIV co-infected*	0.032	Beta(0.2;13.1)	[0.000;0.123]	[30]	
Epidemiology					
Total population, aged 18-100 (2018)					
Senegal	8318000			[47]	Population age structure is divided into 5-year classes
Côte d'Ivoire	12752000				
Cameroon	12622600				
Viremic prevalence					
Senegal	1.3%		[1.1%-1.4%]	[2]	
Côte d'Ivoire	1.3%		[1.1%-1.4%]		
Cameroon	0.7%		[0.5%-0.8%]		
% diagnosed with CHC					
Senegal	6.0%			[1]	Number of people diagnosed with CHC / number of viremic cases
Côte d'Ivoire	6.0%				
Cameroon	4.0%			[24]	
% diagnosed with CHC and treated					
Senegal	2.0%			[1]	Annual number of treated CHC patients / total number of diagnosed cases
Côte d'Ivoire	2.0%				
Cameroon	7.9%			[24]	
Number of patients eligible for treatment					
Senegal	6358				Total population * viremic prevalence * % diagnosed * (1-% treated)
Côte d'Ivoire	9748				
Cameroon	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]	

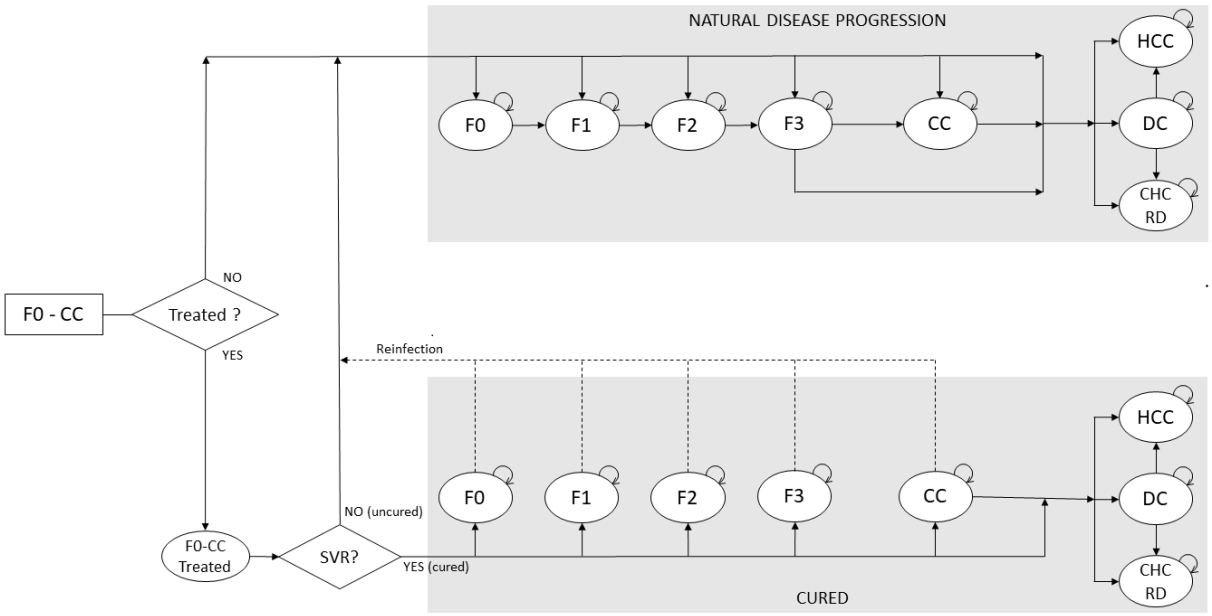
† Life-years saved per patient are calculated as the number of life-years per patient with treatment minus the number of life-years per patient without treatment.

‡ 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

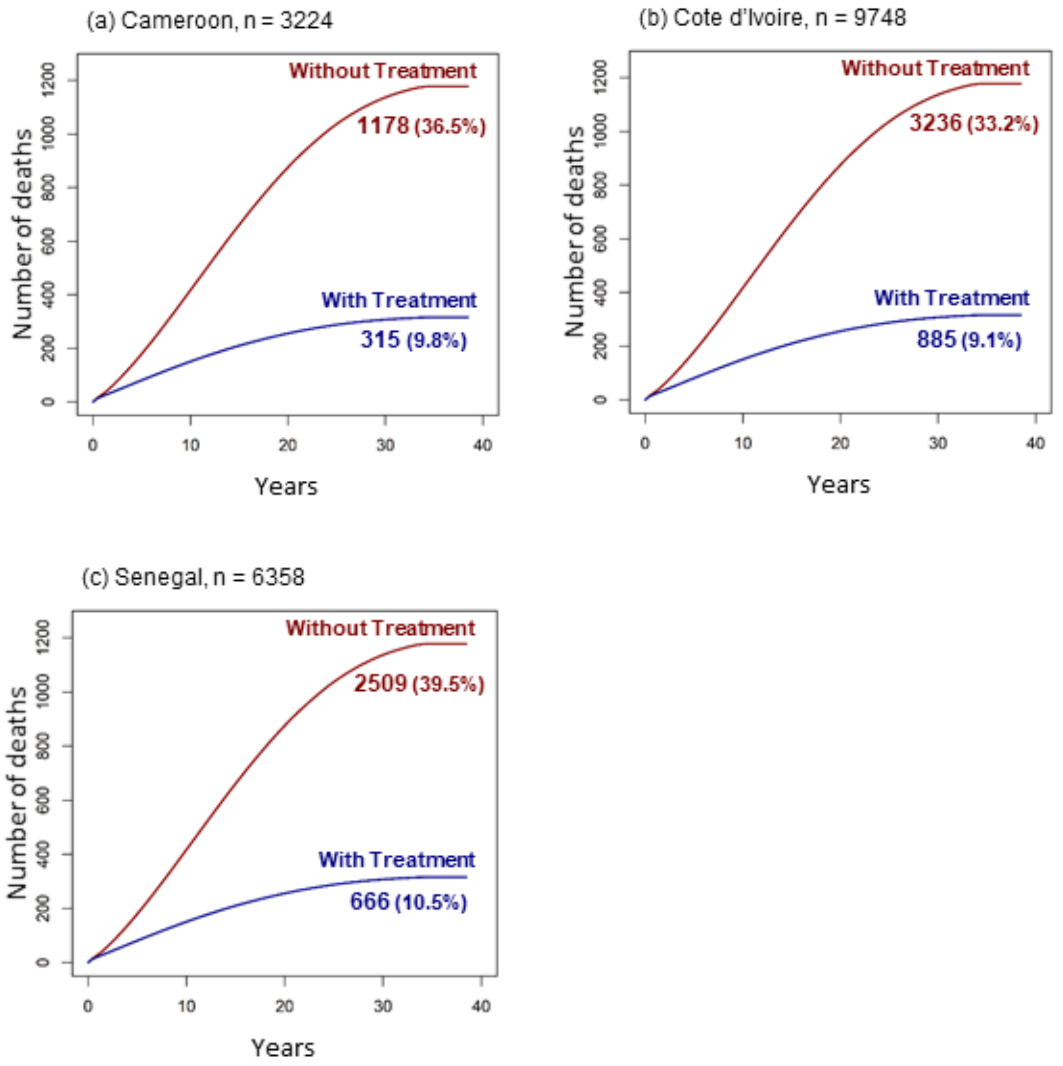
Figure 1: Diagram of the Markov cohort model



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.

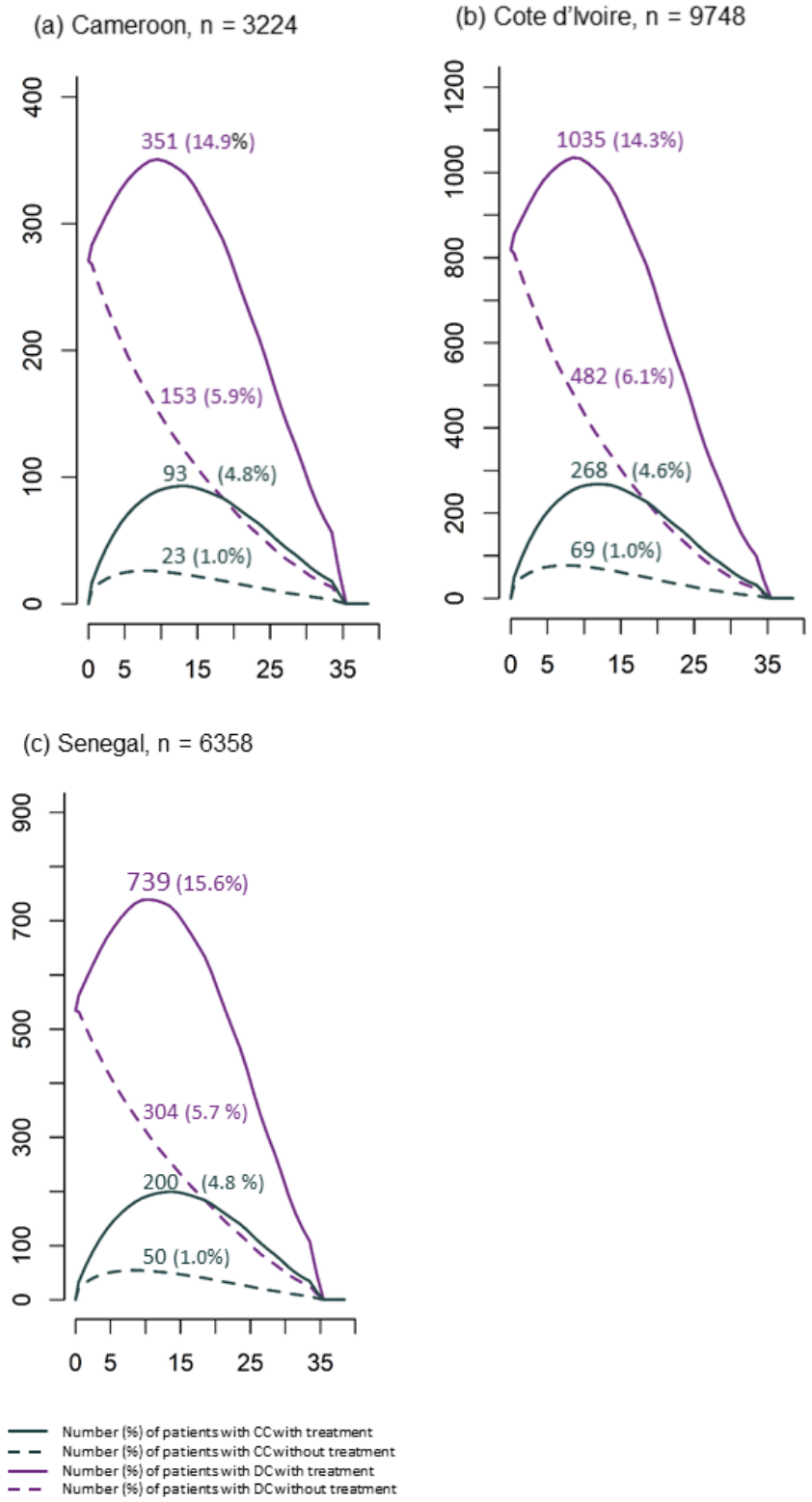
Figure 2: Liver disease-related deaths over lifetime with and without treatment in mono-infected patients diagnosed with chronic hepatitis C in Cameroon (Fig. 2a), Côte d'Ivoire (Fig. 2b) and Senegal (Fig. 2c)



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.