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How to Optimize Hepatitis C Virus Treatment Impact on Life Years Saved in Resource-Constrained Countries

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In resource-constrained countries where the prevalence of hepatitis C virus (HCV) disease is usually high, it is important to know which population should be treated first in order to increase treatment effectiveness. The aim was to estimate the effectiveness of different HCV treatment eligibility scenarios in three different countries. Using a Markov model, we estimated the number of life-years saved (LYS) with different treatment eligibility scenarios according to fibrosis stage (F1-F4 or F3-4), compared to base case (F2-F4), at a constant treatment rate, of patients between 18 and 60 years of age, at stages F0/F1 to F4, without liver complications or coinfections, chronically infected by HCV, and treated with pegylated interferon (IFN)/ribavirin or more-efficacious therapies (i.e. IFN free). We conducted the analysis in Egypt (prevalence = 14.7%; 45,000 patients treated/year), Thailand (prevalence = 2.2%; 1,000 patients treated/year), and Côte d'Ivoire (prevalence = 3%; 150 patients treated/year). In Egypt, treating F1 patients in addition to ≥F2 patients (SE1 vs. SE0) decreased LYS by 3.9%. Focusing treatment only on F3-F4 patients increased LYS by 6.7% (SE2 vs. SE0). In Thailand and Côte d'Ivoire, focusing treatment only on F3-F4 patients increased LYS by 15.3% and 11.0%, respectively, compared to treating patients ≥F2 (ST0 and SC0, respectively). Treatment only for patients at stages F3-F4 with IFN-free therapies would increase LYS by 16.7% versus SE0 in Egypt, 22.0% versus ST0 in Thailand, and 13.1% versus SC0 in Côte d'Ivoire. In this study, we did not take into account the yearly new infections and the impact of treatment on HCV transmission. *Conclusion*: Our model-based analysis demonstrates that prioritizing treatment in F3-F4 patients in resource-constrained countries is the most effective scenario in terms of LYS, regardless of treatment considered. (HEPATOLOGY 2015;62:31-39)

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In the world, 2%-3% of the population is infected by HCV,[1] and liver complications resulting from HCV infection kill almost 500,000 persons per year.[2] In resource-constrained countries, a very low

Abbreviations: ALT, alanine aminotransferase; ANRS, Agence Nationale de Recherche contre le SIDA; DAA, direct-acting antiviral; GDP, gross domestic product; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; Peg-IFN, pegylated interferon; LYS, life-years saved; RR, relative risk; RBV, ribavirin; SC, scenario Côte d'Ivoire; SE, scenario Egypt; SOF, sofosbuvir; ST, scenario Thailand; SVR, sustained virological response; UN, United Nations; USD, U.S. dollars; WHO, World Health Organization.

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proportion of patients have received anti-HCV treatment. However, with the imminent availability of efficacious, better-tolerated, and hopefully affordable new direct-acting antivirals (DAAs), there is an increasing political will to finally test and treat patients with HCV in these countries. In this line of thought, recently, World Health Organization (WHO) launched guidelines for the screening, care, and treatment of persons with hepatitis C infection.[3] The purpose of these guidelines is to serve as a framework that can allow the expansion of clinical services to patients with HCV infection. In this context, it is important to develop strategies to prioritize HCV treatments.

The most concerned geographical areas by hepatitis C epidemic are East and Central Asia, Middle East/North Africa, and sub-Saharan Africa.[4] However, in those regions, there are disparities. Within resource-constrained countries, Egypt, a lower-middle-income country,[5] has the highest prevalence of HCV infection in the world (14.7% of 15-59 years old have anti-HCV antibodies).[6,7] Important efforts are made by the Egyptian government to facilitate access to treatment for infected patients, in particular, by opening national treatment centers. Consequently, from 2006 to 2013, approximately 278,000 patients were treated, which, though being important, remains insufficient when considering the number of patients to be treated. Compared to Egypt, in Thailand, as in Côte d'Ivoire, the situation is different (Table 1). First, in Thailand, the annual gross domestic product (GDP) per capita is higher than Egypt,[8] but the political commitment is lower; in Côte d'Ivoire, part of the same income group as Egypt, political actions are just starting and seem insufficient. Second, in both Thailand and Côte d'Ivoire, the prevalence of the disease is high, although inferior to Egypt, with an estimated prevalence in the general population of 2.2% in Thailand[1,9] and 3% in Côte d'Ivoire.[10] However, the number of HCV-infected patients who are treated is very low, in part related to a lower political commitment than in Egypt. Epidemic situations as well as political and social commitment in those three world regions are diverse and could lead to the necessity of different medical care and treatment.

In a recent study, we showed that treating HCV-infected patients at fibrosis stages F2-F4 in Egypt is effective as well as cost-effective.[11] Regardless of cost and cost-effectiveness issues, in these settings, it is important to know which population should be treated first in order to increase treatment effectiveness. In this study, using a mathematical model, we sought to estimate the impact of different HCV treatment eligibility scenarios on the number of life-years saved (LYS) in these three different settings (Egypt, Thailand, and Côte d'Ivoire) to assist with decision making. We also sought the impact on LYS of more-efficacious therapies and increasing number of patients treated. The choice of countries included in this analysis takes into account heterogeneities in the geographical localization, annual GDP per capita, HCV prevalence, estimated number of HCV patients treated per year, and data availability in particular.

Material and Methods

Model Overview

A previously published Markov model[11] was used to simulate HCV progression among 4 million Egyptian,[6,12,13] 631,000 Thai,[1,14] and 191,000 Ivorian patients[10,14] ages 18-60 years estimated to be chronically infected with HCV, but without any other viral coinfections or history of liver decompensation (Supporting Fig. 1). Dual therapy with pegylated interferon/ribavirin (Peg-IFN/RBV) was introduced into the model of the natural progression of the disease. By contrast to patients who achieved a sustained virological response (SVR) to treatment at stages <F4, those who achieved an SVR at stage F4 remained at risk of developing complications, but at lower rates.[15] In patients who did not achieve an SVR, progression of fibrosis was considered to be the same as that in untreated patients.

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Table 1. Observed Situations on Chronic HCV Infection in Egypt, Thailand, and Côte d'Ivoire

Political commitment	Egypt Yes	Thailand No	Côte d'ivoire No
GDP per capita, $USD (2013)	3,314	5,779	1,521
Estimated prevalence, %	14.7	2.2	3
Estimated number of patients with chronic HCV infection (year of estimation)	4,000,000 (2008)	631,000 (2013)	191,000 (2013)
Number of treatments available per year	45,000	1,000*	150*
Estimated annual treatment rate, %	1.12	0.16	0.08
HCV genotypes (% of viral strains)			
1	0	33	79
2	0	4	14
3	0	53	0
4	100	0	0
5	0	0	7
6	0	10	0

Sources: Previous literature.[1,6-10,12-14]
*Experts' opinion.

Considering that the number of HCV centers and human resources may not increase over time, we hypothesized that 45,000 patients infected with genotype 4 HCV will be treated each year in Egypt, as since 2011. In Thailand and Côte d'Ivoire, we simulated HCV progression of cohorts of patients infected with different HCV genotypes, considering that only 1,000 and 150 patients would be treated per year, respectively (Table 1). For each country, we estimated LYS with different HCV treatment eligibility scenarios assuming that the same number of patients will be treated each year. Patients eligible for treatment in each scenario received Peg-IFN/RBV for 48 weeks in Egypt, where patients are infected with genotype 4, and 24-48 weeks in Thailand and Côte d'Ivoire according to HCV genotype.[16,17] Interferon (IFN)-free regimens were considered in sensitivity analysis.

Eligibility Scenarios

Treatment Scenario. In the three countries, base-case scenarios considered that, from 2014, patients at stages F2-F4 were treated (SE0 for Egypt, ST0 for Thailand, and SC0 for Côte d'Ivoire).

Two alternative scenarios were compared to the base case in the three countries. Scenario 1 (SE1, ST1, and SC1) considered that patients, whatever their fibrosis stage (F1-F4), were eligible for treatment. Scenario 2 (SE2, ST2, and SC2) targeted patients at fibrosis stages F3-F4.

Total Number of Patients Treated. Treatment was carried on for all scenarios over a 20-year period. This led to 1,216,500 patients treated in Egypt (32% of the overall cohort of HCV-infected patients), assumed to be the highest reasonable proportion, 20,000 patients treated in Thailand (3.5% of the cohort), and 3,000 patients treated in Côte d'Ivoire (1.7% of the cohort).

Inputs

Study Population. We assumed that patients chronically infected by HCV in Egypt had the same characteristics at diagnosis as those enrolled in the Agence Nationale de Recherche contre le SIDA (ANRS)-12184 study in Egypt[18] that compares the performance of three noninvasive markers of fibrosis in newly diagnosed patients: 34% of patients were at fibrosis score F0/F1; 33% at F2; 16% at F3; and 17% at F4. In Thailand, we assumed that patients had the same characteristics at diagnosis as those enrolled in the study of Avihingsanon et al.[16]: 56.5% were at fibrosis stage F0/F1; 18.4% at F2; 12.4% at F3; and 12.7% at F4. Finally, in Côte d'Ivoire, characteristics of patients were based on experts' opinion and routine practice: 20% at stage F0/F1; 40% at stage F2; 30% at stage F3; and 10% at stage F4. Fibrosis stage distribution at diagnosis was stratified by age, gender, and abnormal alanine aminotransferase (ALT) level. To override the problem of small numbers, the distribution was obtained from multivariate logistic polytomous regression on fibrosis stage using SAS software (SAS Institute Inc., Cary, NC).

Disease Progression. Probabilities of disease progression were taken from the international literature (Supporting Table 1).[19,20] Background mortality probabilities were derived from United Nations (UN) statistics[13] and WHO statistics.[21]

Treatment Efficacy. Data on HCV treatment efficacy and treatment stopping criteria were derived from an Egyptian publication for genotype 4[22] as well as from the international literature for other genotypes[23-25] (Supporting Table 2). Patients who achieved an SVR at F4 had 87% lower rates of liver-related death (relative risk $[RR]_{F4\rightarrow Death} = 0.13$, RR of death), 92% lower rates of decompensation ($RR_{F4\rightarrow Dec} = 0.08$, RR of decompensation), and 73% lower rate of hepatocellular carcinoma (HCC; $RR_{F4\rightarrow HCC} = 0.27$, RR of HCC).[15]

Table 2. Impact of Base Case and Alternative Treatment Eligibility Scenarios on Total LYS in Egypt

Egypt	Base Case SE0	Scenario 1 SE1	Scenario 2 SE2
Treatment initiation criteria (2014 and after)	F2/F3/F4	F1*/F2/F3/F4	F3/F4
Number of patients treated per year	45,000	45,000	45,000
Baseline analysis[†]			
Total LYS vs. no treatment	2,428,166	2,334,562	2,590,458
Additional total LYS vs. base case, %	–	−3.9	+6.7
Sensitivity analysis			
IFN-free therapy in 2014[‡]			
Total LYS vs. no treatment	3,759,121	3,560,653	4,385,967
Additional total LYS vs. baseline, %	+54.8	+52.5	+69.3
Additional total LYS vs. base case, %	–	−5.3	+16.7
90,000 patients treated/year from 2014[†]			
Total LYS vs. no treatment	2,611,740	2,526,855	2,920,579
Additional total LYS vs. baseline, %	+7.6	+8.2	+12.7
Additional total LYS vs. base case, %	–	−3.3	+11.8
90,000 patients treated/year and IFN-free therapy in 2014[‡]			
Total LYS vs. no treatment	4,057,011	3,819,886	5,037,311
Additional total LYS vs. baseline, %	+67.1	+63.6	+94.5
Additional total LYS vs. base case, %	–	−5.8	+24.2

*Only if elevated ALT level at diagnosis.
[†]SVR = 65% for ≤F2 and 40% for >F2, with Peg-IFN/RBV.
[‡]SVR = 80% whatever the stage, with IFN-free treatment with SOF/RBV.

Sensitivity Analyses

We first assessed the impact of increasing number of treatments available per year while respecting the total number of patients treated stated in baseline analysis (32%). This lead to a treatment period of 10 years. [Correction added on May 4, 2015, after first online publication: first sentence of this paragraph originally ended at "treatments available." The rest of the current first sentence and the second sentence of this paragraph were added.] This analysis was done for Egypt only, where the number of treated patients per year has increased over time and may be still improved in the future. As new, more-efficacious, and less-expensive treatments will be soon available in this country, we estimated that doubling the number of patients treated per year would be reasonable. In Thailand and in Côte d'Ivoire, where the number of treated patients is low and national treatment programs are less developed than in Egypt, we did not perform this sensitivity analysis; indeed, in those countries, even if we double the number of patients treated, the overall number of treated patients will be small.

Given the availability of new efficacious treatments with DAAs in the near future and, more particularly, sofosbuvir (SOF),[26-31] we sought, in addition, to estimate LYS with the same scenarios as in baseline analysis, but with IFN-free-based treatment regimens (Supporting Table 2).

We performed additional sensitivity analyses to evaluate the impact of some of our hypothesis on the results and, in particular, probabilities of disease progression, treatment efficacy, and population distribution at diagnosis. This was only presented for Egyptian analysis; results of Egyptian analyses could be extrapolated to Côte d'Ivoire and Thailand regarding these sensitivity analyses. First, we increased the probability of HCV-related death at F4 from 1% (stage with no varices or ascites) to 3.4% (stage with varices but no ascites) to assess the impact it could have when considering F4 patients for treatment in our alternative scenarios.[19] We also varied probabilities of fibrosis transition and probabilities of cirrhosis complications using upper and lower limits described in the literature.[19,20]

Second, we assessed the impact of an HCV diagnosis at more-advanced stages than considered in our study, and we increased the probability of being at ≥F3 stage for patients >30 years of age at diagnosis, using the upper limit of the confidence intervals of our logistic polytomous regression.

Third, we decreased SVR rates by 20%, considering that they came from a clinical study and might be overestimated.

Finally, given controversial results in the literature on the assumption that patients who achieve an SVR at F4 still have a risk of complications or HCV-related death, we increased simultaneously for all potential complications the RR of progression of the disease in F4 patients with an SVR versus no SVR until it equaled 1, meaning that an SVR after treatment in F4 had no effect on the progression of fibrosis at stage F4. We also tried to identify the combination of RR

Table 3. Impact of Base Case and Alternative Treatment Eligibility Scenarios on Total LYS in Thailand

Thailand	Base Case ST0	Scenario 1 ST1	Scenario 2 ST2
Treatment initiation criteria (2014 and after)	F2/F3/F4	F1*/F2/F3/F4	F3/F4
Number of patients treated per year	1,000	1,000	1,000
Baseline analysis†			
Total LYS vs. no treatment	52,868	46,827	60,964
Additional total LYS vs. base case, %	–	−11.4	+15.3
Sensitivity analysis			
IFN-free therapy in 3 years‡			
Total LYS vs. no treatment	91,324	80,168	111,448
Additional total LYS vs. baseline, %	+72.7	+71.2	+82.8
Additional total LYS vs. base case, %	–	−12.2	+22.0

*Only if elevated ALT level at diagnosis.

†SVR = 63% for ≤F2 and 44% for >F2 for genotype 3 HCV, 46% and 32% for genotype 1 HCV, and 72% and 61% for genotypes 2 and 6 HCV, with Peg-IFN/RBV.

‡SVR = 94% for ≤F2 and 92% for >F2 for genotype 3 HCV, 92% and 80% for genotype 1 HCV, and 100% and 90% for genotypes 2 and 6 HCV, with IFN-free treatment with SOF/RBV.

Table 4. Impact of Base Case and Alternative Treatment Eligibility Scenarios on Total LYS in Côte d'Ivoire

Côte d'Ivoire	Base Case SC0	Scenario 1 SC1	Scenario 2 SC2
Treatment initiation criteria (2014 and after)	F2/F3/F4	F1*/F2/F3/F4	F3/F4
Number of patients treated per year	150	150	150
Baseline analysis†			
Total LYS vs. no treatment	10,811	9,894	12,001
Additional total LYS vs. base case, %	–	−8.5	+11.0
Sensitivity analysis			
IFN-free therapy in 3 years‡			
Total LYS vs. no treatment	18,645	17,062	21,082
Additional total LYS vs. baseline, %	+72.5	+72.4	+75.7
Additional total LYS vs. base case, %	–	−8.5	+13.1

*Only if elevated ALT level at diagnosis.

†SVR = 46% for ≤F2 and 32% for >F2 for genotype 1 HCV, and 72% and 61% for genotypes 2 and 5 HCV, with Peg-IFN/RBV.

‡SVR = 92% for ≤F2 and 80% for >F2 for genotype 1 HCV, and 100% and 90% for genotype 2 and 5 HCV, with IFN-free treatment with SOF/RBV.

values for which the eligibility scenarios became as effective as the base-case scenario.

Results

Baseline Analysis. Table 2 shows total LYS with each scenario versus no treatment and additional total LYS versus base case in Egypt. With SE0, 2,428,166 life-years were saved, compared with no treatment. SE1, including, in addition, F1 patients for treatment, led to a 3.9% decrease in LYS, compared to SE0. Treating only patients at stages ≥F3 (SE2) led to a 6.7% increase in total LYS, compared with SE0. In Thailand, with ST0, 52,868 life-years were saved, compared with no treatment (Table 3). Including patients at stage F1 as eligible for treatment (ST1) led to an 11.4% decrease in number of LYS, compared to ST0. With patients at stages ≥F3 eligible for treatment (ST2), LYS increased by 15.3% versus ST0. In Côte d'Ivoire, 10,811 life-years were saved with SC0, compared with no treatment (Table 4). With SC1, including F1 patients as eligible for treatment, LYS decreased by 8.5%, compared to SC0, but LYS increased by 11.0% with SC2 (≥F3 patients), compared to SC0.

Sensitivity Analysis. In Egypt, taking into account IFN-free regimens increased total LYS versus baseline analysis by 54.8% with SE0 (Table 2). This increase was the highest for scenario treating patients at stages ≥F3 (SE2), when compared to SE0 (16.7% vs. 6.7% in baseline analysis). Increasing the number of patients treated per year by 2-fold while reducing the period of treatment increased LYS by 7.6% with SE0, compared with baseline analysis, and saved 2,611,740 life-years. [Correction added May 4, 2015, after first online publication: preceding sentence was edited to include the words "while reducing the period of treatment" after "Increasing the number of patients treated per year by 2-fold."] Scenarios' impacts, compared to SE0, were more important than in baseline, and SE2 was still the most effective scenario. When, in addition to the increased number of patients treated, we took into account IFN-free regimens, SE2 remained the most effective scenario, when compared to SE0, in sensitivity analysis (+24.2%).

In Thailand, treating with IFN-free regimens in 3 years increased LYS versus baseline analysis by 72.7% with ST0 (Table 3). This increase was the highest for the scenario including only stages ≥F3 for treatment (ST2), and ST2 remained the only effective scenario, compared to ST0 (+22.0%).

In Côte d'Ivoire, treating with IFN-free regimens in 3 years increased LYS versus baseline analysis by 72.5% with SC0 (Table 4). The highest increase was with SC2 including patients at stages ≥F3 for treatment, and SC2 was the most effective scenario, when compared to SC0, in sensitivity analysis (+13.1%).

For Egypt, increasing the probability of death from HCV infection at F4 from 1% to 3.4% increased LYS versus baseline analysis by 29.4% with SE0 (Table 5). Accordingly, the impact of other scenarios, compared to SE0, was decreased: −3.6% versus −3.9% with SE1 and +3.4% versus +6.7% with SE2. Variation in transition probabilities had no impact on the results (Supporting Table 3).

Variation in the RR of disease progression at stage F4 for patients achieving an SVR led to a decrease in LYS with the three scenarios tested (Fig. 1). Also, for other scenarios, differences with SE0 decreased when

Table 5. Sensitivity Analyses on Data Introduced in the Model and Impact on Total LYS in Egypt

Egypt	Base Case SE0	Scenario 1 SE1	Scenario 2 SE2
Treatment initiation criteria (2014 and after)	F2/F3/F4	F1*/F2/F3/F4	F3/F4
Baseline analysis			
Total LYS vs. no treatment	2,428,166	2,334,562	2,590,458
Additional total LYS vs. base case, %	–	−3.9	+6.7
Sensitivity analysis			
Increase in probability of HCV mortality for patients in F4[†]			
Total LYS vs. no treatment	3,140,838	3,026,578	3,247,780
Additional total LYS vs. baseline, %	+29.4	+29.6	+25.4
Additional total LYS vs. base case, %	–	−3.6	+3.4
For patients achieving SVR in F4, no reduction of risks of complication (RR = 1)[‡]			
Total LYS vs. no treatment	1,588,494	1,555,624	1,480,140
Additional total LYS vs. baseline, %	−34.6	−33.4	−42.9
Additional total LYS vs. base case, %	–	−2.1	−6.8
20.0% decrease of treatment efficacy[§]			
Total LYS vs. no treatment	1,965,580	1,889,045	2,102,139
Additional total LYS vs. baseline, %	−19.1	−19.1	−18.9
Additional total LYS vs. base case, %	–	−3.9	+6.9
Fibrosis stage distribution at diagnosis for patients ages more than 30 years[‖]			
Total LYS vs. no treatment	2,514,087	2,429,191	2,646,190
Additional total LYS vs. baseline, %	+3.5	+4.1	+2.2
Additional total LYS vs. base case, %	–	−3.4	+5.3

*Only if elevated ALT level at diagnosis.

[†]3.4% vs. 1%.

[‡]In baseline analysis: In patients achieving SVR in F4 compared to those without SVR or untreated, RR associated with progression from F4 to decompensation = 0.08; RR associated with progression from F4 to HCC = 0.27; RR associated with progression from F4 to death from HCV infection = 0.13.

[§]52.0% vs. 65.0% for ≤F2 and 32.0% vs. 40.0% for >F2.

[‖]Means at more severe stages (≥F3).

the probability of complications in patients with an SVR approached that of patients without an SVR (Fig. 1). However, SE1 was never better than SE0. In the case of probabilities of complications equal to the one of patients without SVR (RR = 1), compared with baseline analysis, LYS decreased by 34.6% with SE0, and SE2 saved fewer lives than SE0 (−6.8% versus +6.7% in baseline) and was the less-effective scenario (Table 5). Also, SE0 was still more effective than SE1 (−2.1% vs. −3.9% in baseline analysis). Treating only patients at stages F3-F4 (SE2) was the most effective scenario for the combination of RRs up to the following values: no risk reduction of HCC ($RR_{F4\rightarrow HCC} = 1$); 43% risk reduction of death ($RR_{F4\rightarrow Death} = 0.57$); and 65% risk reduction of decompensation ($RR_{F4\rightarrow Dec} = 0.35$; Fig. 1). Then, treating patients at stages F2-F4 (SE0) became the most effective scenario. Moreover, SE2 became the less-effective scenario for the combination of RRs above the following values: no risk reduction of HCC ($RR_{F4\rightarrow HCC} = 1$); 14% risk reduction of death ($RR_{F4\rightarrow Death} = 0.86$); and 47% risk reduction of decompensation ($RR_{F4\rightarrow Dec} = 0.53$; Fig. 1).

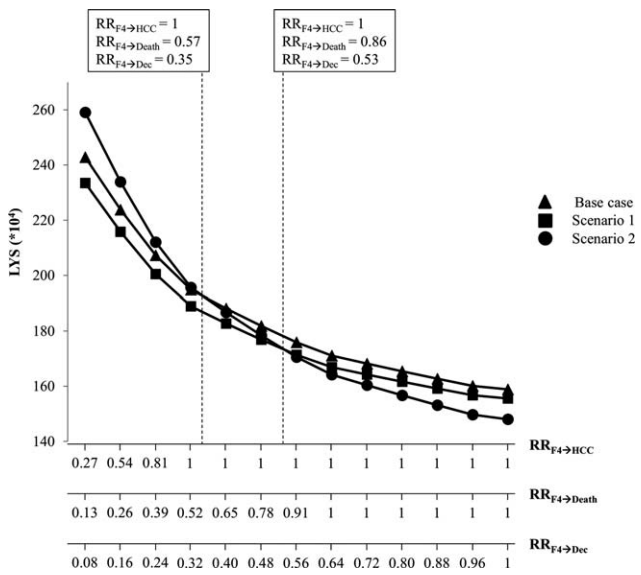

Fig. 1. Impact on LYS of different RRs of disease progression for patients who achieve SVR at stage F4 in Egypt. The graph plots the LYS (y-axis) according to the changing in RRs (risk of disease progression with SVR vs. without SVR) for each scenario. The boxes at top of the graph represent the values of RR for what scenario 2 is as effective as base-case scenario or as effective as scenario 1.

Reducing the efficacy of treatment by 20.0% decreased LYS versus baseline analysis by 19.9% with SE0. However, the scenario's impact remained unchanged (Table 5). Finally, the hypothesis of a more-severe stage distribution at diagnosis, for patients >30 years of age, increased LYS versus baseline analysis, but did not have an impact on scenario efficacy versus SE0.

Discussion

Our model-based analysis shows that treating patients at late fibrosis stages while considering the same current annual treatment rate (45,000 patients per year in Egypt, 1,000 patients in Thailand, and 150 patients in Côte d'Ivoire) would lead to a substantial increase in the total LYS. Treating patients at the severe fibrosis stages of HCV infection has been shown to be cost-effective.[11] This analysis further shows that, with a constant and limited number of treatments, it is more effective to focus treatment on patients at stages F3-F4 with Peg-IFN/RBV or with IFN-free regimens. Our results strengthen the newest published WHO recommendations on treatment against chronic HCV infections, in which it is recommended to treat patients at fibrosis stages F3-F4 in priority when logistic and budget resources are limited.[3] The sensitivity analysis shows that our results are robust to a wide range of variations in our baseline hypothesis, except if an SVR at stage F4 has a minimal impact on the probability of complications or death.

Scenarios considering treatment of patients at stage $\geq$F3 had more impact on LYS, regardless to HCV treatment. However, we demonstrated that our results on the impact of treating patients at late stage of the disease are mainly owing to the assumption that treatment has an impact on disease progression in F4 patients who achieve an SVR. It is not realistic to think that there would be no slowing of disease progression in patients at F4 stage who achieve an SVR. Therefore, we searched the combination of values of RR of disease progression in patients with an SVR versus no SVR for which treating patients at stages $\geq$F3 did not impact LYS. In our model-based study, when we considered the case of Egypt, the scenario including patients at stage F1 (SE1) was never the most effective scenario, whatever the RRs considered. The scenario considering patients at stage $\geq$F3 eligible for treatment (SE2) remained the most effective scenario when simultaneously RRs were the following: $RR_{F4\rightarrow HCC}$ equaled 1; $RR_{F4\rightarrow Death}$ was <0.57; and $RR_{F4\rightarrow Dec}$ was <0.35. For RR above those values, the scenario including F2 patients in the eligibility criteria was the most effective. SE2 was the less-effective scenario when simultaneously RRs were the following: $RR_{F4\rightarrow HCC}$ equaled 1; $RR_{F4\rightarrow Death}$ was >0.86; and $RR_{F4\rightarrow Dec}$ was >0.53. In Singal et al.'s meta-analysis of the literature from 1966 to 2008 on these three RRs in F4 HCV-infected patients with an SVR, the maximum RR was 0.23 for death, 0.35 for HCC, and 0.56 for decompensation.[15] In another study, Morgan et al. also reported that SVR in F4 patients leads to a reduction of liver-related morbidities and mortalities, compared with patients not treated,[32] and these results were consistent with those of Singal et al. Therefore, our baseline results are reasonable, even though studies evaluating the impact of an SVR on complications and especially decompensation should be conducted in resource-constrained countries.

We illustrated that considering more-efficacious treatments, including SOF in the case of Egypt, Thailand, or Côte d'Ivoire, does not change our conclusions and means that even with a better response to treatment, but with limited number of treatment slots, treatment must be given to patients at severe stages in priority. This is important given that new DAAs and, in particular, SOF will be soon available as routine treatments for chronic HCV in resource-limited countries, with an affordable price. For example, in Egypt, the price of a 12-week regimen of SOF seems to be between $1,000 and $1,500 U.S. dollars (USD), which is lower than the current price of dual therapy with Peg-IFN/RBV for 48 weeks.[27]

We also showed that with an increased number of treatment slots, more life-years would be saved and more specifically if patients at late stages of the disease are treated in priority. In our analysis, doubling the number of patients treated per year in Egypt led to an increase of 8% to 13% of LYS, according to the different scenarios. Moreover, focusing treatment on F3/F4 patients was found to have a higher impact on life years saved than focusing treatment on F1/F1 patients. Indeed, treating the same number of patients, but for a shorter period, has a more important impact for patients at severe stages of the disease given that they are treated before they progress to liver complications or become too old to be treated according to national treatment guidelines. However, pursuing these efforts on a longer period would lead to a much higher increase of life years saved because of a higher number of patients treated. Such analysis should be realized using a dynamic population of patients rather than a cohort. [Correction added May 4, 2015, after first publication: the preceding four sentences were added to this paragraph.] We could have expected a more important impact. This can be explained by, first, the fact that doubling the number of patients treated in Egypt results in an increased number of patients treated (from 32% to 57%), but among patients with chronic infections overall and not specifically those at late stage of the disease. As showed in our analysis, focusing treatment on F3/F4 patients will have a higher impact on LYS than focusing treatment on F0/F1 patients. Second, treatment efficacy is of 65% for F0-F2 patients and 40% for F3-F4 patients in Egypt; we do not consider a second-line treatment for nonresponders and relapsers who continue to have an additional risk of dying from HCV chronic infection. Finally, even in F4 patients with SVR, we still have a risk of disease progression to complications and death.

We did not test the impact of increasing the number of treatment slots available per year in Thailand or Côte d'Ivoire owing to the fact that national treatment programs are less developed in those countries. We can

anticipate that increasing the number of treatments would lead to an increase in the number of LYS, but the increase of treatment slots available should be much more important than doubling the number of patients treated per year to observe an impact on LYS. Also, in Thailand, where the current available treatment is Peg-IFN/RBV, the cost for HCV drugs to treat 1 patient is estimated at $17,800 versus $2,000 USD in Egypt,[33] and in Côte d'Ivoire, this treatment is estimated to cost $14,950 USD. The challenge in the future will be to make available IFN-free regimens at a low and affordable cost; this will make easier treatment scale-up. It is also important to mobilized sponsors and local governments to develop research, prevention, screening, and treatment programs to reduce the burden of HCV in resource-constrained countries and eradicate HCV infection.[34]

Our analysis had several limitations. First, we did not take into account new yearly infections, although the virus is continuing to spread, leading to a high prevalence and also a high incidence of the disease.[35] As a result, we did not consider the impact of treatment on ongoing transmission of HCV infection. This was mainly demonstrated in the literature for high-risk "transmitters," such as people undergoing frequent iatrogenic procedures[35] or people who inject drugs, treatment reducing HCV prevalence and transmission.[36] Consequently, if we had considered HCV transmission in our model, increasing treatments would avoid a higher number of liver deaths and increase the number of LYS. Recently, Wedermeyer et al. demonstrated that increasing treatments with more-efficacious regimens could lead, in Egypt, to a 95% decrease of HCV viremic people and a 75% decrease of HCV mortality by 2030.[37] However, in their analysis, the researchers considered that up to 350,000 patients were treated per year and over a period of 17 years. Therefore, they assumed that the proportion of patients tested for their HCV and who are in care is extremely high.[37] In 2008,[6] only 3.8% of the Egyptian population ages 15-59 were ever tested for HCV. To be able to reach the amount of 350,000 patients treated per year, as assumed in the analysis of Wedemeyer et al., in Egypt, there is a need to expand HCV screening programs and, consequently, linkage to care. In addition, it is important to increase the number of treated patients among those tested and linked to care; a majority of HCV chronically infected patients are waiting to be treated. In addition, it is not clear that under the current situation, because of logistic issues such as manpower, but also organizational issues, treatment could be provided to 350,000 patients. Thus, under the current situation and based on the proportion of infected patients currently treated, HCV treatment impact on transmission will be probably low.

Second, in our analysis, we demonstrated that with the same number of available treatments, treating patients at late stages of the disease was more effective than treating patients at earlier stages. Implementing such strategy implies to have F3-F4–sensitive diagnostic methods. If not, some patients at late stages would decompensate before being considered for treatment. This was taken into account in our model, given that not all patients at stage F3-F4 were treated.

Third, we used data from either international studies, studies with small sample sizes in low-income countries, or experts' opinion to assess fibrosis stage distribution at diagnosis and fibrosis progression; this could not reflect the cohort of HCV-infected patients in Egypt, Thailand, or Côte d'Ivoire. However, this was tested in a sensitivity analysis and it had no impact on the conclusions. Fourth, the model developed was for HCV monoinfected patients and we therefore did not considered human immunodeficiency virus (HIV)-HCV coinfected patients in Thailand and Côte d'Ivoire. Some studies report that the prevalence of cirrhosis in coinfected patients is more important and fibrosis progression more rapid,[16,38] and it would be interesting to study the impact of our treatment scenarios for such a population. However, increasing fibrosis transition probabilities or varying fibrosis stage distribution at diagnosis (Table 5 and Supporting Table 2) had no impact on our conclusions. We can then think that our results could be applicable for patients coinfected with HIV. Finally, data on the use of IFN-free regimens are scarce in low-income countries. Also, in our model, we used treatment response described in clinical trials in which adherence to treatment must be much higher than in real-life settings. However, our sensitivity analysis showed that varying treatment efficacy, and, in particular, decreasing it, had a minimal impact on our overall conclusions.

In conclusion, in resource-constrained countries, it is important to develop strategies to prioritize HCV treatments. This will be even more important when efficacious, better-tolerated, and hopefully affordable new DAAs will be available. Our study demonstrates that in Egypt, Thailand, or Côte d'Ivoire, where a limited number of treatment slots and HCV treatment centers are available, it would be more effective to treat patients at the severe stages of HCV infection, regardless of the HCV treatment nature. Our analysis could probably be extrapolated to other low-income countries with a high HCV prevalence.

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Supporting Information

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