Available online at http://scik.org
Commun. Math. Biol. Neurosci. 2020, 2020:82
https://doi.org/10.28919/cmbn/4996
ISSN: 2052-2541

OPTIMAL CONTROL FOR A DISCRETE MODEL OF HEPATITIS C WITH LATENT, ACUTE AND CHRONIC STAGES IN THE PRESENCE OF TREATMENT

LAHCEN EL YOUSSOUFI[1,*], HAJAR MOUTAMANNI[1], ABDERRAHIM LABZAI[1], OMAR BALATIF[2], MOSTAFA RACHIK[1]

[1]Laboratory of Analysis, Modeling, and Simulation (LAMS),Department of Mathematics and Computer Science,Faculty of Sciences Ben M'Sik, Hassan II University of Casablanca. BP 7955, Sidi Otheman, Casablanca, Morocco

[2]Laboratory of Dynamical Systems,Mathematical Engineering Team (INMA), Department of Mathematics, Faculty of Sciences El Jadida, Chouaib Doukkali University, El Jadida, Morocco

Abstract. In this article, we consider a discrete mathematical model of viral hepatitis C (HCV). The population we will study is divided into six compartments: the unawareness susceptible, awareness susceptible, exposed individuals, individuals with acute infection, individuals with chronic infection and the individuals undergoing treatement. Our objective is to find the best strategy to reduce the number of the unawareness susceptible, individuals with chronic infection and exposed individuals through three controls, respectively, education and awareness, access to early detection and treatment. We study the impact of each control mechanism individually and the impact of combinations of these strategies in the control of HCV. A discret version of Pontryagin's maximum principle was used to characterize the optimal controls obtained. Numerical simulation of the results, using MATLAB software, showed the effectiveness of the proposed controls, and the results confirm the performance of the proposed optimization strategies.

Keywords: optimal control; Hamiltonian; objective function; PCR; Pontryagin's maximum principle; HCV.

2010 AMS Subject Classification: 93A30.

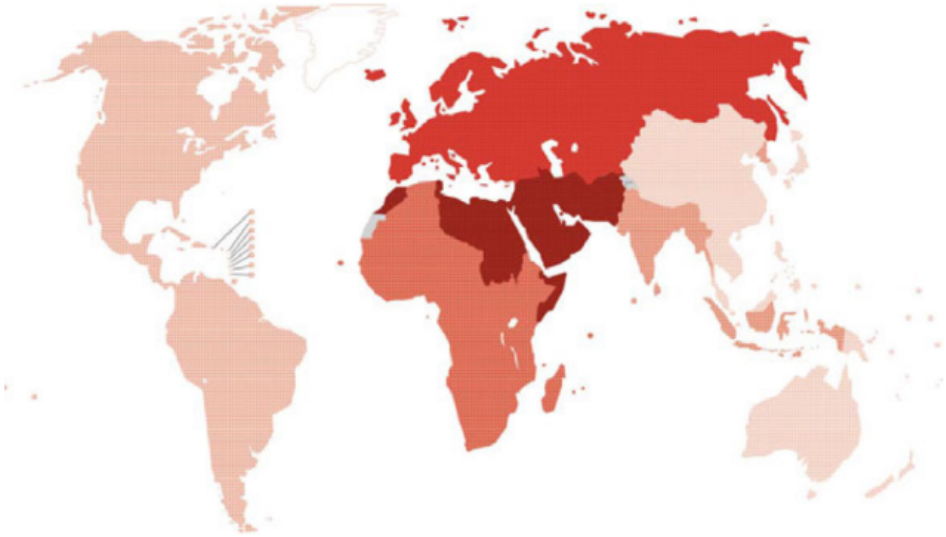
*Corresponding author

E-mail address: elyoussoufilahcen5@gmail.com

Received September 3, 2020

1. INTRODUCTION

The World Health Organization (WHO) report confirms that viral hepatitis is an international public health problem comparable to other major communicable diseases such as HIV, tuberculosis and malaria. Despite the heavy burden it places on people in all parts of the world, hepatitis was not really considered a health and development priority until recently. It will no longer be neglected with the adoption of the resolution on the programme for sustainable development to 2030. This strategy addresses the five hepatitis viruses (hepatitis A, B, C, D and E), with a special focus on hepatitis B and C because of the relative high public health burden. In particular, the third goal specifically calls for action to combat viral hepatitis [2]. Hepatitis C HCV was diagnosed in 1989 after the discovery of a non-HBV and non-HAV liver pathogen [7]. Under WHO in Global hepatitis report 2017 ≪ Viral hepatitis caused 1.34 million deaths in 2015, a number comparable to deaths caused by tuberculosis and higher than those caused by HIV. However, the number of deaths due to viral hepatitis is increasing over time, while mortality caused by tuberculosis and HIV is declining. Most viral hepatitis deaths in 2015 were due to chronic liver disease (720 000 deaths due to cirrhosis) and primary liver cancer (470 000 deaths due to hepatocellular carcinoma). Globally, in 2015, an estimated 257 million people were living with chronic HBV infection, and 71 million people with chronic HCV infection. The epidemic caused by HBV affects mostly the WHO African Region and the western pacific region. The epidemic caused by HCV affects all regions, with major differences between and within countries. The WHO Eastern Mediterranean Region and the European Region have the highest reported prevalence of HCV≫.[20]



Incidence of HCV infection

		Incidence rate (per 100 000)		Total number (000)	
WHO region	Map key	Best estimate	Uncertainty interval	Best estimate	Uncertainty interval
African Region		31.0	22.5–54.4	309	222–544
Region of the Americas		6.4	5.9–7.0	63	59–69
Eastern Mediterranean Region		62.5	55.6–65.2	409	363–426
European Region		61.8	50.3–66.0	565	460–603
South-East Asia Region		14.8	12.5–26.9	287	243–524
Western Pacific Region		6.0	5.6–6.6	111	104–124
Global		23.7	21.3–28.7	1 751	1 572–2 120

FIGURE 1. Incidence of HCV infection in the general population, by WHO region, in 2015, 1.75 million new infections in 2015 [20]

FIGURE 2. Estimated global number of deaths due to viral hepatitis, HIV, malaria and TB,2000–2015 [19]

HCV is an RNA virus with a variety of fairly large genomes. There are six main genotypes, noted from 1 to 6, and numerous subtypes. These genotypes are not responsible for significantly different evolutions of hepatitis. Regardless of genotype, cure with the newer AAD treatments is achieved in most cases in 8 to 12 weeks.hepatitis C is a liver disease caused by a virus. Hepatitis C is a liver disease caused by a virus. Acute and chronic liver ionization of varying severity, ranging from a mild form that lasts a few weeks to a severe illness that lasts a lifetime 1. The risk of reinfection remains a possibility after clearance of acute hepatitis C.Spontaneous resolution of chronic hepatitis C is relatively rare, but can occur.This silent disease often progresses with few symptoms,even during advanced stages of disease [11].

The hepatitis C virus (HCV) is a major human pathogen that infects 3% of the world's population. The long-term impact of HCV infection is highly variable, ranging from minimal changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma (HCQ) [16] . The initial infection is often asymptomatic and the virus is eliminated by the host immune system in approximately 25% of cases. In the remaining 75%, the virus persists in the host and the infection becomes chronic [16, 17].

The high number of chronically infected people and the lack of a vaccine indicate that treatment will be part of the control of the disease. The hepatitis C virus is transmitted primarily through blood, and the most common modes of infection result from exposure to small amounts of blood, occurring through injection drug use, unsafe injections, unsafe care, and transfusion of blood or blood products for which there has been no screening. Worldwide, approximately 71 million people are chronic carriers of hepatitis C. Approximately 399,000 people die each year from hepatitis C, mostly from cirrhosis or hepatocellular carcinoma. For a significant number of people with the chronic form of the disease, the infection progresses to cirrhosis or cancer of the liver [2, 18]. The Nineties is the period of the first treatments and therapeutic trials, the development of screening tests, the first recommendations for screening and treatment and the structuring of the healthcare offer. In terms of screening, ELISA tests for the detection of anti-HCV antibodies (Ac) of the 3rd generation, which are highly sensitive and specific, were developed as early as 1993. High-performance tests for the detection of HCV RNA in serum by PCR (polymerase chain reaction) were developed and used in clinical practice [8]. Research by

Moroccan laboratories has contributed to the global fight against this human virus. Hepatitis C patients in Morocco now have access to effective local treatments at relatively low cost, thanks to the production of generics of the principle drugs in the country. However, access to screening and biological tests remains largely insufficient. The cause: prices! This is the point of the study published by the Association de lutte contre le sida (ALCS), "Diagnosis and monitoring of viral hepatitis C in Morocco - State of play, strategies for universal access", including an international comparison with 20 countries with similar socio-economic profiles.

On December 10, 2015, the generic SSB 400, a revolutionary Sofosbuvir-based treatment to cure hepatitis C, made its debut in Morocco. Since then, this generic drug, marketed by Pharma Laboratories 5 [14], is available at a lower cost: 3,000 dirhams per box per month of treatment, for a total cost of 9,000 DH (Moroccan dirhams). A price almost 100 times lower than that of Sovaldi, an originator drug, whose overall cost of treatment is estimated at 800,000 dirhams in other countries[8].

However,complementary drugs are necessary to ensure a complete cure for the disease,and access to treatment at the national level is still insufficient,as is the situation in most developing countries around the world.

To understand the effect of prevention,awareness,early detection,access to treatment and the effectiveness of treatment on the transmission and dynamics of viral hepatitis C,we propose a discrete mathematical model with six compartments containing the stages of infection:non-infectious exposure,acute infected and chronically infected with treatment, while introducing three controls u_1, u_2 et u_3.

It should be noted that mathematical modeling of HCV has been studied by many researchers [4, 13]. We observe that most of those researchers focused on the continuous time models described by the differential equations.It is noted that,in recent years, more and more attention has been given to discrete time models [10, 21, 23].The reasons for adopting discrete modeling are as follows :Firstly, the statistical data are collected at discrete moments (day, week, month, or year).It is more direct and more accurate and timely to describe the disease using discrete time models than continuous time models. Secondly, the use of discrete time models can avoid

some mathematical complexities such as choosing a function space and regularity of the solution. Thirdly,the numerical simulations of continuous time models are obtained by the way of discretization.In this paper,we considered an (unawareness susceptible, awareness susceptible, exposed, acute infected, chronic infected and the individuals undergoing treatement) model for HCV with varying population seize.

Our model S_nS_aEICT is a modified and extended version of the HCV model presented in [4] with the inclusion of the latent stage, represented by the exposed population, by adding a third control u_3 representing acces to early detecttion , which will lead to early treatement later, in the case of the individual's test is positive.Also in our article we have considered a discrete model, in order to dertemine the optimal strategy for the control of the disease in a discret time. The paper is organised as follows:in section 2, the mathematical model is proposed. In section 3 we investigate the optimal control problem for the proposed discrete mathematical model. In the 4th section the numerical simulation was dealt with, using MATLAB.in the 5th section we discussed various possible strategies, using the proposed controls, to combat the HCV epidemic. The conclusion is given in section 6.

2. Formulation of the Mathematical Model

We are interested in our work by a mathematical model with six compartments S_nS_aEICT. The awareness susceptible S_a are less exposed to the attraction of the HCV virus, compared to those of S_n, thanks to their knowledge through advertising, education, prevention. The S_a also comes from the recoveries of the T compartment. Generally, it is thought that the acute phase is more infectious than the chronic one,and the chronic one is more than the treated one. So $k1$ and $k2$ are used to denote the infectiousness of chronic and treated individuals relative to acute infections ($k1 > k2$). The E exposures are in the incubation period for the HCV virus, generally are asymptomatic, 80% are asymptomatic among the infected, they are healthy carriers. In some cases an infected person may spontaneously recover from the disease during the E, I or C phases (between 25% and 40% for the E and I classes), but spontaneous recovery is relatively rare for the chronically ill C. Contamination of susceptible individuals S_n and S_a is essentially through contact with infected patients from the I, C and T compartments, hence the coefficients λ_{S_n} and λ_{S_a} representing contact.

2.1. Description of the Model.

- **The compartment** S_n represents **the unawareness susceptible** these are individuals at risk of infection who do not have information about hepatitis C and its severity. They have never been to prevention sessions. It also contains the category of illiterates and newborns. Individuals in the S_n compartment can move on to S_a by ω, the latter is a rate moving from unawareness susceptible to awareness class.So, in general, individuals in the S_n compartment are more likely to be infected with the virus than those in the S_a. Contamination in individuals from compartment S_n is by contact with a sick individual from one of the compartments I, C or T
- **The compartment** S_a,these are **the awareness susceptible**, refers to the compartment of potentially infected individuals who already have information about viral hepatitis C or who have attended awareness and prevention sessions on this subject. Contamination in individuals from compartment S_a is By contact with a sick individual from one of the compartments I, C or T. Note that:the two groups S_n and S_a include, mainly, people who change blood especially during transfusion, people with chronic diseases other than hepatitis C, AIDS patients, the elderly, people with other types of viral hepatitis (for example the HBV type). The S_a compartment can also contain the medical staff caring for hospitalized patients undergoing hepatitis C treatment.
- **The compartment** E, these are **the exposed**, this compartment represents exposed individuals who are in the incubation period of the epidemic, subjects during this phase are asymptomatic, and they are generally infected but not infectious. The incubation period for hepatitis C ranges from 2 weeks to 6 months. After initial infection, approximately 80% of individuals are asymptomatic, they are healthy carriers. ε is the rate of transmission from the E class to the I class. Individuals in this compartment are considered carriers of a low viral load of the HCV virus. Early detection tests will be applied locally in urban or rural areas where HCV infection is considered very high, i.e. where the reproductive rate R_0 is higher than the national average, and in places where people are sick, such as hospitals, homes and workplaces [8].

- **The compartment** I, these are **the acute infected**, this compartment includes individuals who have acute viral hepatitis C infections. In general, this phase of the infection has a short duration, after this period the patient passes to the chronic phase at a rate of 75% [1] otherwise the patient heals spontaneously. Symptoms may include fever, fatigue, lack of appetite, nausea, vomiting, abdominal pain, darker colored urine, grayish stool, joint pain and jaundice (yellowing of the skin and whites of the eyes)[8].
- **The compartment** C, these are **the chronically infected**, this compartment groups together individuals who have chronic viral hepatitis C infections, during this phase the virus can take a lifelong hold. The θ coefficient represents the mortality rate of chronic individuals due to hepatitis C after having reached cirrhosis during the terminal stage of this viral disease. Approximately 30% (15-45%) of infected individuals will spontaneously shed the virus within 6 months of infection without receiving any treatment and the remaining 70% (55-85%) of infected individuals will progress to the chronic form of the disease. Among these chronic patients,the risk of cirrhosis of the liver is 15 to 30% over a period of 20 years[15].
- **The compartment** T, these are **the individuals undergoing treatement**, represents individuals who are undergoing treatment who are not yet cured or individuals cured and established after having undergone the adopted therapeutic protocol. Patients undergoing treatment who are not cured may infect susceptible individuals of both classes S_n and S_a(For example, infection of a person in the caring body after contact with a host-bound patient...). A patient of T can be cured after following the prescribed treatment with a percentage ranging from 85% to 98%. If the patient is cured, then he joins the class of individuals S_a with a transfer rate $(1-p)*\xi$ otherwise if there are complications he returns to the class of chronic individuals C with the rate $p*\xi$.

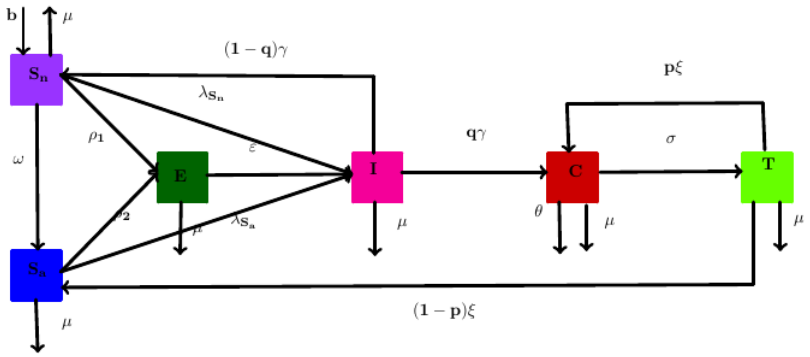


FIGURE 3. Diagram of transitions between epidemiological classes.

2.2. Model Equations. According to the characteristics of HCV transmission illustrated in Figure 3, the model is given by the following system of ordinary differential equations:

$$
(1)\qquad \begin{cases}
S_{n,k+1} = S_{n,k} + b - \rho_1 S_{n,k} - \lambda_{S_n} S_{n,k} - (\mu+\omega) S_{n,k} + (1-q)\gamma I_k \\
S_{a,k+1} = S_{a,k} + \omega S_{n,k} - \rho_2 S_{a,k} - \lambda_{S_a} S_{a,k} - \mu S_{a,k} + (1-p)\xi T_k \\
E_{k+1} = E_k + \rho_1 S_{n,k} + \rho_2 S_{a,k} - (\mu+\varepsilon) E_k \\
I_{k+1} = I_k + \lambda_{S_n} S_{n,k} + \lambda_{S_a} S_{a,k} + \varepsilon E_k - (\mu+\gamma) I_k \\
C_{k+1} = C_k + q\gamma I_k - (\mu+\sigma+\theta) C_k + p\xi T_k \\
T_{k+1} = T_k + \sigma C_k - (\mu+\xi) T_k
\end{cases}
$$

where

$$\lambda_{S_n} = \beta(I_k + k_1 C_k + k_2 T_k) \qquad\qquad \lambda_{S_a} = \alpha \lambda_{S_n}$$

The parameters used in our model are defined as follows:

TABLE 1. Definitions of parameters used in model (1)

Parameters	Description
b	birth rate
μ	death rate
β	transmission coefficient
k_1	infectiousness of chronic infections relative to acute ones
k_2	infectiousness of treated individuals relative to acute ones
α	infectiousness of awareness susceptible relative to unawareness ones
ω	rate moving from unawareness susceptible to awareness class
γ	rate leaving acute infection class
q	proportion of progressing to chronic state from acute state
ξ	rate transferring from treated stage
p	proportion of moving back to chronic state from treated class
σ	rate moving from chronic class to treated class
θ	HCV indueed death rrate
ρ_1	rate moving from unawareness susceptible to exposed class
ρ_2	rate moving from awareness susceptible to exposed class
ε	rate moving from exposed class to infected class

3. THE OPTIMAL CONTROL PROBLEM

In this section, we discuss the optimal control of our model,which consists mainly of analyzing the measures adopted to control viral hepatitis C. The state and non-governmental organizations(NGOs)can adopt a strategic plan by applying precautionary measures focusing mainly on publicity and prevention(through the internet, radio, awareness sessions, TV,... etc), access to early detection and treatment,in order to fight against this pathogen at a lower cost. In our model $u_{1,k}$ represents the control that reflects efforts to inform and educate the susceptible population S_n, which is unaware of the seriousness of HCV hepatitis. $u_{2.k}$ is used to denote the application and evaluation of the effectiveness of treatment given to individuals with chronic

conditions. $u_{3,k}$ represents a control to facilitate access to early detection and thus access to early treatment for individuals in compartment E(exposed), who are in the incubation period, there by reducing or eradicating their viral load and suspending their access to the acute or chronic infectious phase. Assuming $0 \leq u_i \leq 1$, and u_i being a measurable function, $i = 1,2,3$. The form of the optimal control depends on the analyzed system, the objective function being optimized. The model is given as follows:

$$
(2)\quad \begin{cases}
S_{n,k+1} = S_{n,k} + b - \rho_1 S_{n,k} - \lambda_{S_n} S_{n,k} - (\mu + u_{1,k}) S_{n,k} + (1-q)\gamma I_k \\
S_{a,k+1} = S_{a,k} + u_{1,k} S_{n,k} - \rho_2 S_{a,k} - \lambda_{S_a} S_{a,k} - \mu S_{a,k} + (1-p)\xi T_k \\
E_{k+1} = E_k + \rho_1 S_{n,k} + \rho_2 S_{a,k} - (\mu + u_{3,k}) E_k \\
I_{k+1} = I_k + \lambda_{S_n} S_{n,k} + \lambda_{S_a} S_{a,k} + u_{3,k} E_k - (\mu + \gamma) I_k \\
C_{k+1} = C_k + q\gamma I_k - (\mu + \theta + u_{2,k}) C_k + p\xi T_k \\
T_{k+1} = T_k + u_{2,k} C_k - (\mu + \xi) T_k
\end{cases}
$$

$$
\lambda_{S_n} = \beta (I_k + k_1 C_k + k_2 T_k) \qquad\qquad \lambda_{S_a} = \alpha \lambda_{S_n}
$$

The problem we face here is how to minimize the objective function:

$$
(3)\quad J(u_{1,k}, u_{2,k}, u_{3,k}) = E_{t_f} + I_{t_f} + C_{t_f} + T_{t_f} + \sum_{k=0}^{t_f - 1} (E_k + I_k + C_k + T_k + B_1 \frac{u_{1,k}^2}{2} + B_2 \frac{u_{2,k}^2}{2} + B_3 \frac{u_{3,k}^2}{2})
$$

Where the parametre $B_1 > 0$, $B_2 > 0$ and $B_3 > 0$ are the cost coefficients; they are selected to weigh the relative importance of $u_{1,k}$, $u_{2,k}$ and $u_{3,k}$ at time k. t_f is the final time. On the other hand, we look for optimal $u_{1,k}^*$, $u_{2,k}^*$ and $u_{3,k}^*$ controls such as:

$$
(4)\quad J\left(u_{1,k}^*, u_{2,k}^*, u_{3,k}^*\right) = \min_{(u_{1,k}, u_{2,k}, u_{3,k}) \in U_{ad}} J(u_{1,k}, u_{2,k}, u_{3,k})
$$

where U_{ad} is the set of admissible controls defined by:

$$
(5)\quad U_{ad} = \left\{ \left(u_{1,k}, u_{2,k}, u_{3,k}\right) : a \leq u_{1,k} \leq m, c \leq u_{2,k} \leq d, e \leq u_{3,k} \leq f; k = 0, 1, 2 \ldots t_f - 1, u_{i,k} mesurable \right\}
$$

The sufficient condition for the existence of optimal checks $(u_{1,k}, u_{2,k}, u_{3,k})$ for problems (2) and (3) comes from the following theorem, as in [1, 3, 22]

Theorem 1. *There exists an optimal control* $(u^*_{1,k}, u^*_{3,k}, u^*_{2,k})$ *such that*

$$J(u^*_{1,k}, u^*_{3,k}, u^*_{2,k}) = \min_{(u_{1,k},u_{3,k},u_{2,k})\in U_{ad}} J(u_{1,k}, u_{3,k}, u_{2,k})$$

subjet to the control system (2) with initial conditions.

Proof. Since the coefficients of the state equations are bounded and there are a finite number of time steps $Sn\,Sa$, $E\,I$, C, T are uniformly bounded for all $(u_{1,k}, u_{3,k}, u_{2,k})$ in the control set U_{ad}; thus $J(u_{1,k}, u_{3,k}, u_{2,k})$ is bounded for all $(u_{1,k}, u_{3,k}, u_{2,k}) \in U_{ad}$.
Since $J(u_{1,k}, u_{3,k}, u_{2,k})$ is bounded,

$$\inf_{(u_{1,k},u_{3,k},u_{2,k})\in U_{ad}} J(u_{1,k}, u_{3,k}, u_{2,k})$$

is finite, and there exists a sequence $(u^j_{1,k}, u^j_{3,k}, u^j_{2,k}) \in U_{ad}$ such that

$$\lim_{j\to+\infty} (u^j_{1,k}, u^j_{3,k}, u^j_{2,k}) = \inf_{(u_{1,k},u_{3,k},u_{2,k})\in U_{ad}} J(u_{1,k}, u_{3,k}, u_{2,k})$$

and corresponding sequences of states

$$S^j_n \to S_n$$

$$S^j_a \to S_a$$

$$E^j \to E$$

$$I^j \to I$$

$$C^j \to C$$

$$T^j \to T$$

Since there is a finite number of uniformly bounded sequences, there exist $(u^*_{1,k}, u^*_{3,k}, u^*_{2,k}) \in U_{ad}$ and $(S^*_n,\, S^*_a,\, E^*,\, I^*,\, C^*,\, T^*) \in \mathbb{R}^{T+1}$ such that, on a subsequence,

$$(u^j_{1,k}, u^j_{3,k}, u^j_{2,k}) \to (u^*_{1,k}, u^*_{3,k}, u^*_{2,k})$$

Finally, due to the finite dimensional structure of system (2) and the objective function $J(u_{1,k}, u_{2,k}, u_{3,k})$, $(u^*_{1,k}, u^*_{3,k}, u^*_{2,k})$ is an optimal control with corresponding states $(S^*_n,\, S^*_a,\, E^*,\, I^*,\, C^*,\, T^*)$. Therefore

$$\min_{(u_{1,k},u_{3,k},u_{2,k})\in U_{ad}} J(u_{1,k}, u_{3,k}, u_{2,k})$$

□

We use the method of Pontryagin's principle of discrete-time maximums given in [6, 10, 12]. This principle translates (2)and (4) and (3) into a problem of minimization of a Hamiltonian H_k at time step k defined by:

$$\begin{aligned}
H_k &= L(S_{n,k}, S_{a,k}, E_k, I_k, C_k, T_k) + \sum_{i=1}^{6} \lambda_{i,k+1} f_{i,k+1} \\
&= L(S_{n,k}, S_{a,k}, E_k, I_k, C_k, T_k) + \lambda_1[S_{n,k} + b - \rho_1 S_{n,k} - \lambda_{S_n} S_{n,k} - (\mu + u_{1,k}) S_{n,k} + (1-q)\gamma I_k] \\
&+ \lambda_2[u_{1,k} S_{n,k} + S_{a,k} - \rho_2 S_{a,k} - \lambda_{S_a} S_{a,k} - \mu S_{a,k} + (1-p)\xi T_k] \\
&+ \lambda_3[E_k + \rho_1 S_{n,k} + \rho_2 S_{a,k} - (\mu + u_{3,k}) E_k] \\
&+ \lambda_4[I_k + \lambda_{S_n} S_{n,k} + \lambda_{S_a} S_{a,k} + u_{3,k} E_k - (\mu + \gamma) I_k] \\
&+ \lambda_5[C_k + q\gamma I_k - (\mu + \theta + u_{2,k}) C_k + p\xi T_k] \\
&+ \lambda_6[T_k + u_{2,k} C_k - (\mu + \xi) T_k]
\end{aligned}$$

where

$$L(S_{n,k}, S_{a,k}, E_k, I_k, C_k, T_k) = E_k + I_k + C_k + T_k + B_1 \frac{u_{1,k}^2}{2} + B_2 \frac{u_{2,k}^2}{2} + B_3 \frac{u_{3,k}^2}{2} \tag{6}$$

where $f_{i,k+1} (i = 1,2,3,4,5,6)$ designates the right side of the system (2), and $\lambda_i (i = 1,2,3,4,5,6)$ are the adjoint variables verifying the following theorem:

Theorem 2. *Given an optimal control* $\left(u_{1,k}^*, u_{2,k}^*, u_{3,k}^* \right) \in U_{ad}$ *and the solutions* $S_{n,k}^*, S_{a,k}^*, E_k^*, C_k^*$, *and* T_k^* *of the corresponding state system (2), there exist adjoint functions* $\lambda_{1,k}, \lambda_{2,k}, \lambda_{3,k}, \lambda_{4,k}, \lambda_{5,k}$, *and* $\lambda_{6,k}$ *satisfying*

$$\lambda_{1,k} = \lambda_{1,k+1}[1-\rho_1-\lambda_{S_n}-(\mu+u_{1,k})]+\lambda_{2,k+1}u_{1,k}+\lambda_{3,k+1}\rho_1+\lambda_{4,k+1}\lambda_{S_n}$$

$$\lambda_{2,k} = \lambda_{2,k+1}[1-\rho_2-\lambda_{S_a}-\mu]+\lambda_{3,k+1}\rho_2+\lambda_{4,k+1}\lambda_{S_a}$$

$$\lambda_{3,k} = 1-\lambda_{3,k+1}[-1+\mu+u_{3,k}]+\lambda_{4,k+1}u_{3,k}$$

$$\begin{aligned}\lambda_{4,k} = {} & 1+\lambda_{1,k+1}[-\beta S_{n,k}+(1-q)\gamma]-\lambda_{2,k+1}\alpha\beta S_{a,k}-\lambda_{4,k+1}[-1+\beta S_{n,k}+\alpha\beta S_{a,k}+\mu+\gamma] \\ & +\lambda_{5,k+1}q\gamma\end{aligned}$$

$$\begin{aligned}\lambda_{5,k} = {} & 1-\lambda_{1,k+1}k1\beta S_{n,k}-\lambda_{2,k+1}k1\alpha\beta S_{a,k}+\lambda_{4,k+1}[k1\beta S_{n,k}+k1\alpha\beta S_{a,k}] \\ & -\lambda_{5,k+1}[-1+\mu+\theta+u_{2,k}]+\lambda_{6,k+1}u_{2,k}\end{aligned}$$

$$\begin{aligned}\lambda_{6,k} = {} & 1+\lambda_{1,k+1}k2\beta S_{n,k}+\lambda_{2,k+1}[-k2\alpha\beta S_{a,k}+(1-p)\xi]+\lambda_{4,k+1}[k2\beta S_{n,k}+k2\alpha\beta S_{a,k}] \\ & +\lambda_{5,k+1}p\xi-\lambda_{6,k+1}[-1+\mu+\xi]\end{aligned}$$

With the transversality conditions at time $t_f, \lambda_{1,t_f} = \lambda_{5,t_f} = \lambda_{2,t_f} = \lambda_{3,t_f} = \lambda_{4,t_f} = \lambda_{5,t_f} = 1$ Furthermore, for $k = 0,1,2\ldots t_f-1$ the optimal controls $u^*_{1,k}, u^*_{2,k}$, and $u^*_{3,k}$ are given by :

$$u^*_{1,k} = min\{max\{\frac{1}{B_1}(\lambda_1-\lambda_2)S^*_{n,k}, a\}, m\} \tag{7}$$

$$u^*_{3,k} = min\{max\{\frac{1}{B_3}(\lambda_3-\lambda_4)E^*_k, e\}, f\} \tag{8}$$

$$u^*_{2,k} = min\{max\{\frac{1}{B_2}(\lambda_5-\lambda_6)C^*_k, c\}, d\} \tag{9}$$

Proof. The Hamiltonian at time step k is given by :

$$\begin{aligned}H_k &= E_k+I_k+C_k+T_k+B_1\tfrac{u^2_{1,k}}{2}+B_2\tfrac{u^2_{2,k}}{2}+B_3\tfrac{u^2_{3,k}}{2}+\sum_{i=1}^{6}\lambda_{i,k+1}f_{i,k+1} \\ &= E_k+I_k+C_k+T_k+B_1\tfrac{u^2_{1,k}}{2}+B_2\tfrac{u^2_{2,k}}{2}+B_3\tfrac{u^2_{3,k}}{2} \\ &+\lambda_1[S_{n,k}+b-\rho_1 S_{n,k}-\lambda_{S_n}S_{n,k}-(\mu+u_{1,k})S_{n,k}+(1-q)\gamma I_k] \\ &+\lambda_2[u_{1,k}S_{n,k}+S_{a,k}-\rho_2 S_{a,k}-\lambda_{S_a}S_{a,k}-\mu S_{a,k}+(1-p)\xi T_k] \\ &+\lambda_3[E_k+\rho_1 S_{n,k}+\rho_2 S_{a,k}-(\mu+u_{3,k})E_k]\end{aligned}$$

$$+\lambda_4[I_k+\lambda_{S_n}S_{n,k}+\lambda_{S_a}S_{a,k}+u_{3,k}E_k-(\mu+\gamma)I_k]$$

$$+\lambda_5[C_k+q\gamma I_k-(\mu+\theta+u_{2,k})C_k+p\xi T_k]$$

$$+\lambda_6[T_k+u_{2,k}C_k-(\mu+\xi)T_k]$$

For $k=0,1\ldots t_f-1$ the optimal controls $u_{1,k},u_{2,k},u_{3,k}$ can be solved from the optimality condition,

$$\begin{aligned}\frac{\partial H_k}{\partial u_{1,k}}&=0,\\ \frac{\partial H_k}{\partial u_{2,k}}&=0,\\ \frac{\partial H_k}{\partial u_{3,k}}&=0.\end{aligned}\tag{10}$$

That means:

$$\begin{aligned}\frac{\partial H_k}{\partial u_{1,k}}|_{u_{1,k}}&=B_1u_{1,k}-\lambda_1S_{n,k}+\lambda_2S_{n,k}=0\\ \frac{\partial H_k}{\partial u_{3,k}}|_{u_{3,k}}&=B_3u_{3,k}-\lambda_3E_k+\lambda_4E_k=0\\ \frac{\partial H_k}{\partial u_{2,k}}|_{u_{2,k}}&=B_2u_{2,k}-\lambda_5C_k+\lambda_6C_k=0\end{aligned}$$

It's easy to get:

$$u_{1,k}=\tfrac{1}{B_1}(\lambda_1-\lambda_2)S_{n,k}$$

$$u_{3,k}=\tfrac{1}{B_3}(\lambda_3-\lambda_4)E_k$$

$$u_{2,k}=\tfrac{1}{B_2}(\lambda_5-\lambda_6)C_k$$

However, for $i=1,2,3$, the control attached to this case will be eliminated and removed. By the bounds in U_{ad} of the controls, it is easy to obtain $u^*_{1,k},u^*_{2,k}$, and $u^*_{3,k}$ in the form of (7-8-9). □

4. Numerical Simulation

4.1. Algorithm. In this section, we present the results obtained by solving numerically the optimality system. This system consists of the state system, adjoint system, initial and final time conditions, and the controls characterization. So, the optimality system is given by the following steps:

- **Step 1** $S_{n,0} = s_{n,0}, S_{a,0} = s_{a,0}, E_0 = e_0, I_0 = i_0, C_0 = c_0, \lambda_{1,T} = 0\ \lambda_{2,T} = 0, \lambda_{3,T} = 1, \lambda_{4,T} = 1, \lambda_{5,T} = 1, \lambda_{6,T} = 1$ and given $u^*_{k,0}\ v^*_{k,0}$, and $w^*_{k,0}$
- **Step 2** For $k = 0; 1; \ldots; T-1$ do:

$$S_{n,k+1} = S_{n,k} + b - \rho_1 S_{n,k} - \lambda_{S_n} S_{n,k} - (\mu + u_{1,k}) S_{n,k} + (1-q)\gamma I_k$$

$$S_{a,k+1} = S_{a,k} + u_{1,k} S_{n,k} - \rho_2 S_{a,k} - \lambda_{S_a} S_{a,k} - \mu S_{a,k} + (1-p)\xi T_k$$

$$E_{k+1} = E_k + \rho_1 S_{n,k} + \rho_2 S_{a,k} - (\mu + u_{3,k}) E_k$$

$$I_{k+1} = I_k + \lambda_{S_n} S_{n,k} + \lambda_{S_a} S_{a,k} + u_{3,k} E_k - (\mu + \gamma) I_k$$

$$C_{k+1} = C_k + q\gamma I_k - (\mu + \theta + u_{2,k}) C_k + p\xi T_k$$

$$T_{k+1} = T_k + u_{2,k} C_k - (\mu + \xi) T_k$$

$$\lambda_{1,k} = \lambda_{1,k+1}[1 - \rho_1 - \lambda_{S_n} - (\mu + u_{1,k})] + \lambda_{2,k+1} u_{1,k} + \lambda_{3,k+1}\rho_1 + \lambda_{4,k+1}\lambda_{S_n}$$

$$\lambda_{2,k} = \lambda_{2,k+1}[1 - \rho_2 - \lambda_{S_a} - \mu] + \lambda_{3,k+1}\rho_2 + \lambda_{4,k+1}\lambda_{S_a}$$

$$\lambda_{3,k} = 1 - \lambda_{3,k+1}[-1 + \mu + u_{3,k}] + \lambda_{4,k+1} u_{3,k}$$

$$\lambda_{4,k} = 1 + \lambda_{1,k+1}[-\beta S_{n,k} + (1-q)\gamma] - \lambda_{2,k+1}\alpha\beta S_{a,k} - \lambda_{4,k+1}[-1 + \beta S_{n,k} + \alpha\beta S_{a,k} + \mu + \gamma] + \lambda_{5,k+1} q\gamma$$

$$\lambda_{5,k} = 1 - \lambda_{1,k+1} k1\beta S_{n,k} - \lambda_{2,k+1} k1\alpha\beta S_{a,k} + \lambda_{4,k+1}[k1\beta S_{n,k} + k1\alpha\beta S_{a,k}] - \lambda_{5,k+1}[-1 + \mu + \theta + u_{2,k}] + \lambda_{6,k+1} u_{2,k}$$

$$\lambda_{6,k} = 1 + \lambda_{1,k+1} k2\beta S_{n,k} + \lambda_{2,k+1}[-k2\alpha\beta S_{a,k} + (1-p)\xi] + \lambda_{4,k+1}[k2\beta S_{n,k} + k2\alpha\beta S_{a,k}] + \lambda_{5,k+1} p\xi - \lambda_{6,k+1}[-1 + \mu + \xi]$$

$$u^*_{1,k+1} = min\{max\{\frac{1}{B_1}(\lambda_1 - \lambda_2) S^*_{n,k}, a\}, m\}$$

$$u^*_{2,k+1} = min\{max\{\frac{1}{B_2}(\lambda_5 - \lambda_6) C^*_k, c\}, d\}$$

$$u^*_{3,k+1} = min\{max\{\frac{1}{B_3}(\lambda_3 - \lambda_4) E^*_k, e\}, f\}$$

end for

TABLE 2. The description of parameters used for the definition of discrete time systems (1). We used arbitrary academic data.

$s_{n,0}$	$s_{a,0}$	e_0	i_0	c_0	t_0	ρ_1	ρ_2	β	γ	σ
10^3	10^2	10^2	950	650	90	0.0000003	0.00013	0.0002	0.004	0.08
μ	b	q	p	ξ	$k1$	$k2$	θ	α	ε	ω
0.0000031	0.012	0.00001	0.5	0.5	0.5	0.2	0.0001	0.001	0.00001	0.0002

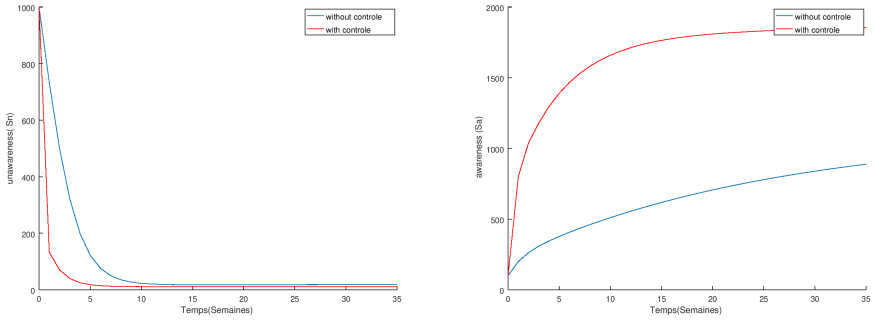


FIGURE 4. the unawareness susceptible Sn , awareness susceptible S_a with all three controls

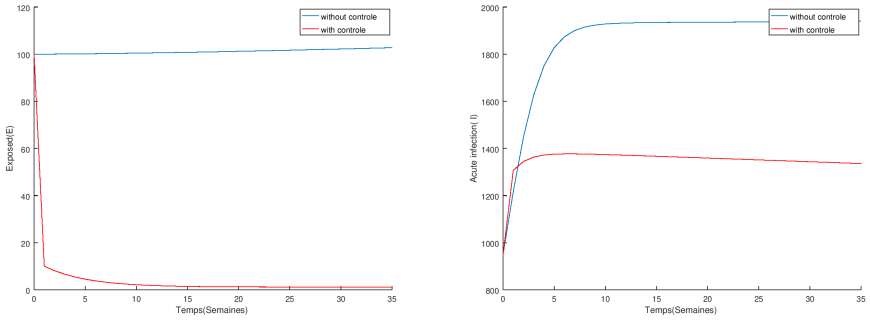


FIGURE 5. the exposed E , the acute infection I with all three controls

5. DISCUSSION

In this section,we study and analyze numerically the effects of certain strategies using one,two,or three of the controls $u_{1,k}$,$u_{2,k}$,and $u_{3,k}$.The strategies considered yield different results.

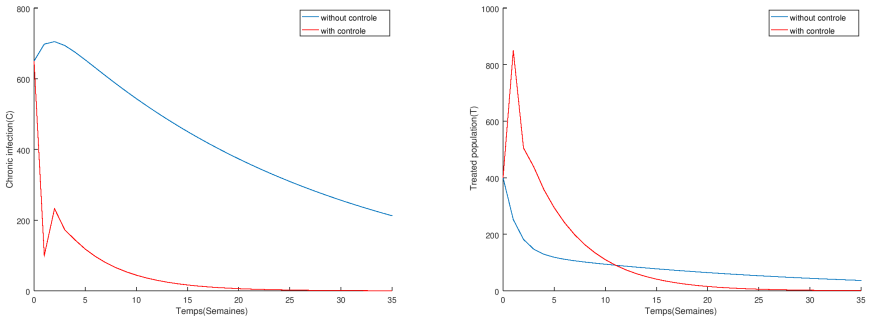


FIGURE 6. chronic infection C, treated population T with all three controls

5.1. Strategy A: Control with Unawareness. Among the efforts that must be made by the state and NGOs(non-governmental organizations)to control the transmission and dynamics of hepatitis C is prevention,which takes the form of information,publicity and awareness raising among the susceptible population S_n,which is ignorant of the seriousness of hepatitis HCV. Figure 7 compares the evolution of the number of individuals in this class with and without the control $u_{1,k}$ in which the effect of prevention through the different media channels has contributed,remarkably,to decrease the number of individuals in this class of the population(S_n)from the first week,but the contamination of individuals remains probable.We note a direct impact on the number of individuals in S_a which is increasing.

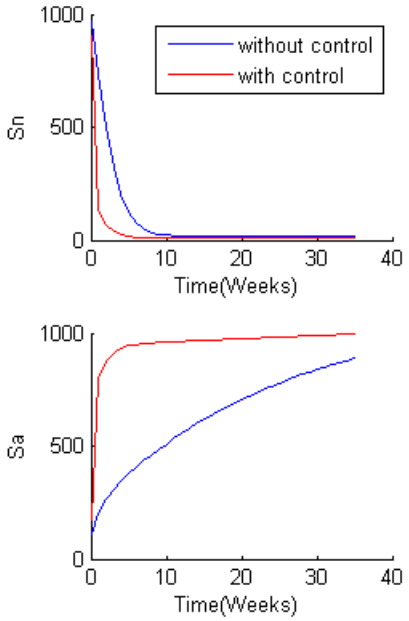


FIGURE 7. The evolution of the unawareness susceptible with and without controls $u_1 \neq 0$,$u_2 = u_3 = 0$

5.2. Strategy B: Control with Treatment. When the number of sick people is so high it is mandatory to use the usual and normal strategy to fight any epidemic,which is treatment,in order to stop the spread of the virus and reduce the number of sick people,mainly those who are in the chronic stage.We propose,therefore,a strategy using a therapeutic protocol with the available drugs,this is interpreted by the control $u_{2,k}$.From the curve (see figure 8) we observe an interesting decrease in the number of individuals chronically affected by the virus from the fourth week. From the twelfth week we notice a progressive decrease in the number of chronically infected individuals, thanks to the efficiency of the available drugs, their number will be negligible after the twentieth week.we notice at the beginning a temporary increase in the number of T individuals who are under treatment just after access to treatment, which is logical.But from the tenth week onwards their number (that of T) will decrease,because if the patient is cured, then he joins the class of individuals S_a with a transfer rate $(1-p)*\xi$ else he returns to the class of chronic individuals C with the rate $p*\xi$.

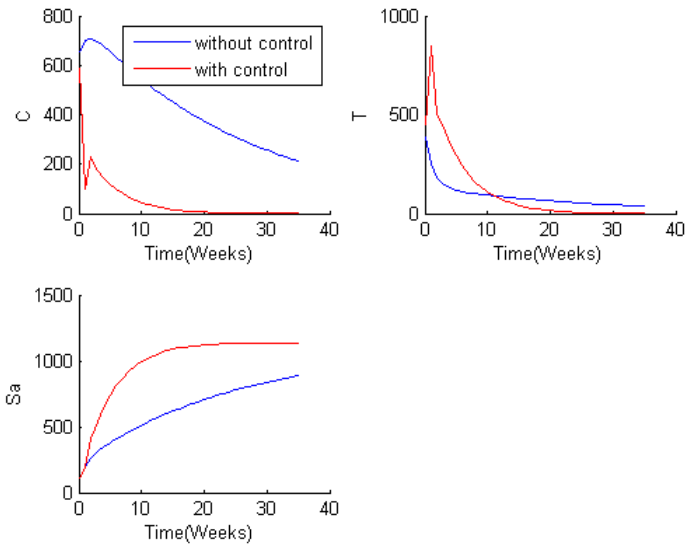


FIGURE 8. The evolution of the chronic infection with and without controls.

$$u_2 \neq 0, u_1 = u_3 = 0$$

5.3. Strategy C: Control with exposed. In this strategy,we study the difference in the evolution of the number of exposed individuals E in the absence and presence of the control $u_{3,k}$ which gives access to early detection and thus to treatment at the appropriate time.The E class are in the incubation period of hepatitis C and they are generally asymptomatic.There is a very significant decrease in the number of individuals of this class who are carriers of the virus as early as the second week after detection.When the viral load is not very high,the exposed individuals E do not become infectious.From the curve (Figure 9)we remarque an immediate decrease in the number of individuals in this compartment from the first weeks of the screening test(For exemple the PCR test or other tests),and from the tenth week onwards their number(E) becomes negligible.The positive effect of the early detection test for HCV hepatitis translates into the possibility of access to early treatment later on.

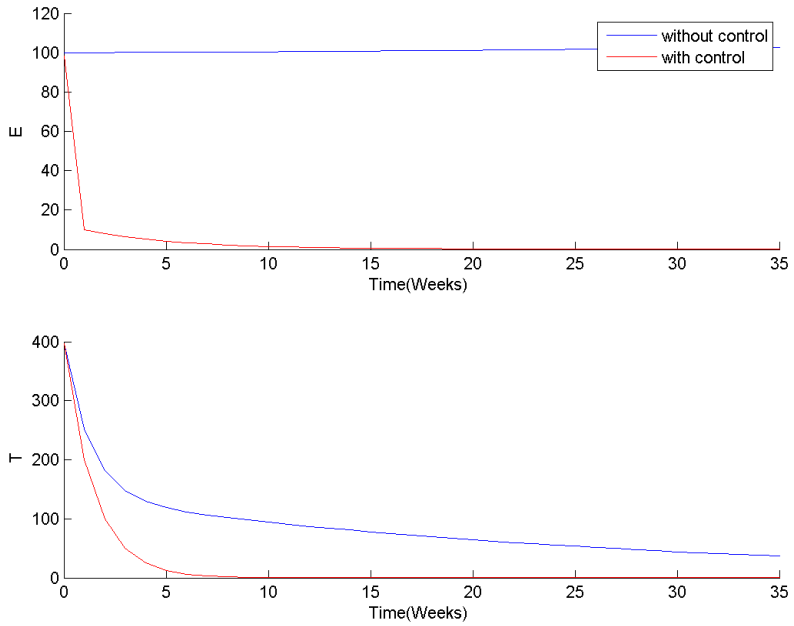


FIGURE 9. The evolution of the exposed with and without controls

$$u_3 \neq 0, u_1 = u_2 = 0$$

5.4. Strategy D: Control with Unawareness and Treatment. This time we combined the two strategies A and B by applying the two controls $u_{1,k}$ and $u_{2,k}$ to compare with the above and try to eventually obtain better results(Figure 10).We find that the numbers of susceptible S_n and chronically infected C are decreasing.There is a significant increase in the number of susceptible S_a in the first week, as individuals from S_n will move directly to the S_a compartment.S_n and S_a are inversely proportional (from S_n to S_a) when the $u_{1,k}$ control is applied.This combination of the two controls remains more effective compared to the use of only one of the two controls.

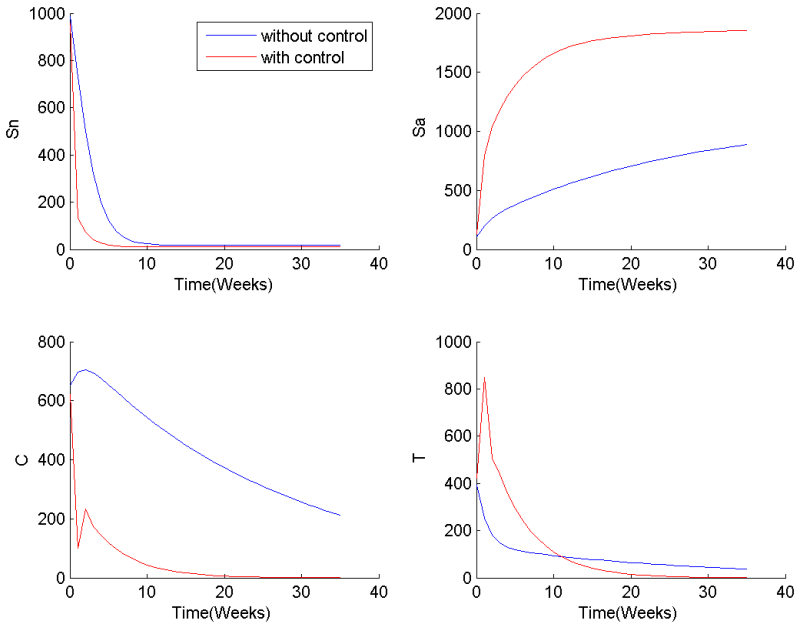


FIGURE 10. Simulations of the HCV model showing the effects of the optimal control in case $u_1 \neq 0$, $u_2 \neq 0$, $u_3 = 0$

5.5. Strategy E: Control with exposed and Treatment. In this strategy, we only used the two controls $u_{3,k}$ and $u_{2,k}$ to compare to the above and try to get possibly better results.We find that the numbers of exposed E and the chronically infected C are decreasing (Figure 6)but this strategy has no impact on susceptible S_n,but we remarque that there is a slight increase in the number of susceptible S_a because a part of the cured individuals T,coming from C after treatment,will pass to compartmentS_a.

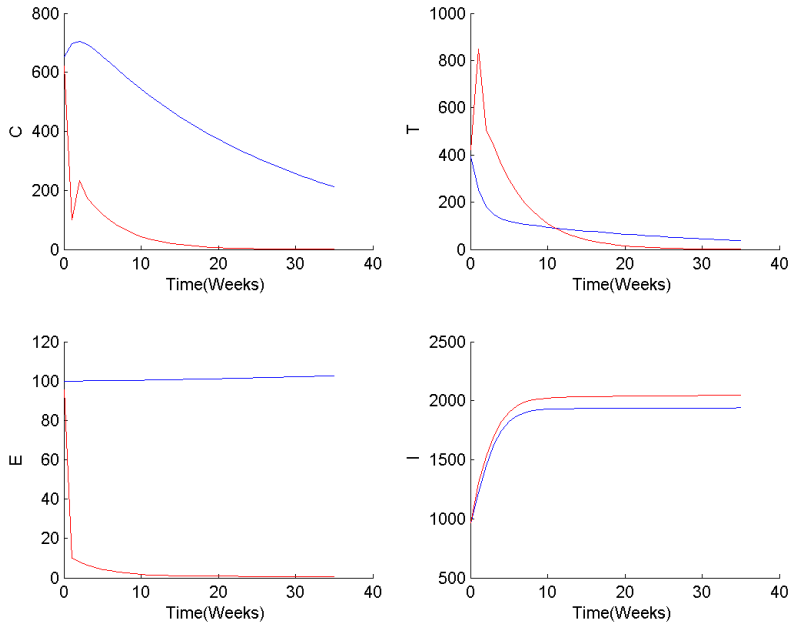


FIGURE 11. Simulations of the HCV model showing the effects of the optimal control in case $u_1 = 0$, $u_2 \neq 0$, $u_3 \neq 0$

5.6. Strategy F: Control with exposed and Unawareness. In this strategy, we combined the two strategies A and C through the application of the two controls $u_{1,k}$ and $u_{3,k}$ representing prevention and early detection, respectively (See Figure12).We note that the number of exposed E and susceptible S_n are decreasing but this strategy does not necessarily have an impact on C compartmnt in the absence of treatment, it underscores the importance of management for treatment after a positive test.But we note that there is an increase in the number of susceptible S_a because application of $u_{1,k}$ requires the change from S_n to S_a, which is obvious.

5.7. Strategy G: Control with exposed,Unawareness and traitement. In this strategy, we combined the three controls at the same time $u_{1,k}$, $u_{3,k}$ and $u_{2,k}$, representing prevention, early detection and treatment (see Figure13).We found that this strategy provides effective control of the spread of the HCV virus.Indeed We found that the number of susceptible S_n, exposed E and chronically infected C immediately decreases during the first two weeks. From the eleventh week the number of susceptible S_n becomes negligible, the detection of healthy exposed E

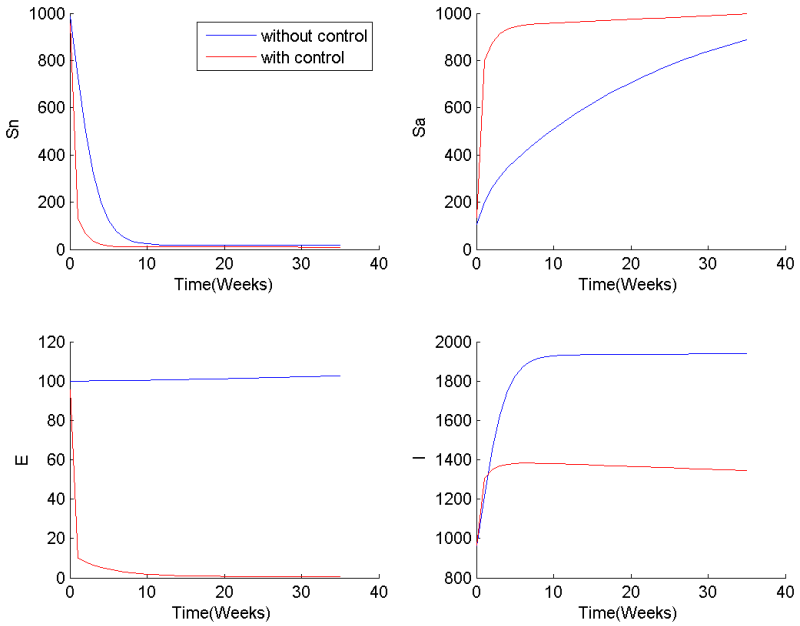


FIGURE 12. Simulations of the HCV model showing the effects of the optimal control in case $u_1 \neq 0$, $u_2 = 0$, $u_3 \neq 0$

immediately decreased this class of individuals during the first week.the call for the 3 controls gave an automatic positive impact on all the other states S_a, I and T, which highlights the effectiveness of this strategy compared to the others considered previously.

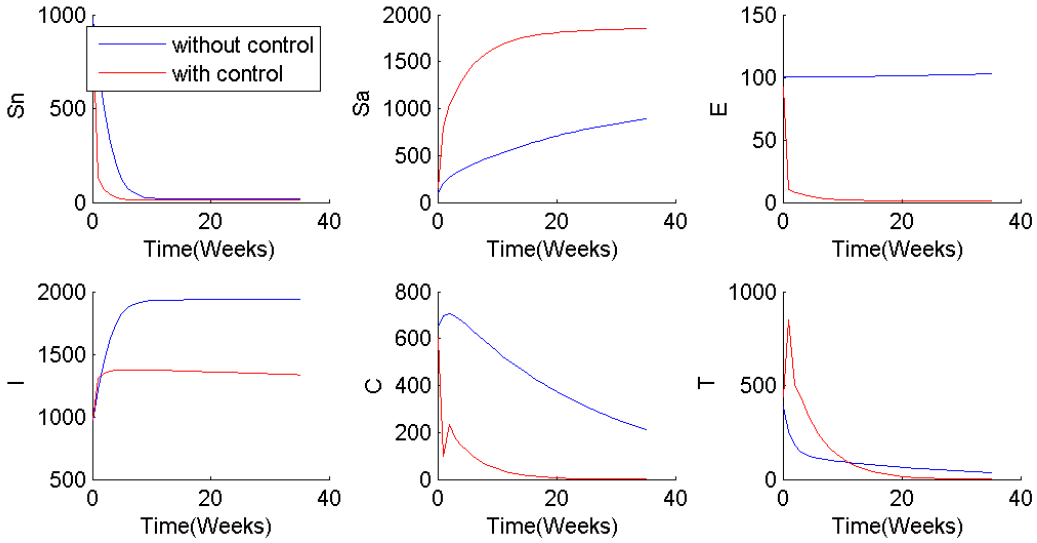


FIGURE 13. Simulations of the HCV model showing the effects of the optimal control in case $u_1 \neq 0$,$u_2 \neq 0$ and $u_3 \neq 0$

6. CONCLUSION

In this work, we have introduced a discrete model of Viral hepatitis C (HCV) by dividing the population into six compartments, in order to minimize the number of chronic diseases, the number of unawareness susceptible individuals and the number of exposed that are generally in a latent period for the virus. We have also introduced three controls that, respectively, represent a control of prevention through the media and other channels, a second control to facilitate access to early detection, and a third control for treatment. The results of the optimal control theory were applied. A discrete version of Pontryagin's Maximum Principle was used to characterize the optimal controls obtained. Numerical simulation of the results, using MATLAB software, showed the effectiveness of the proposed controls and the various proposed strategies especially when we proceed by a combination of the three controls.

CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

REFERENCES

[1] A. Labzai, M. Rachik, O. Balatif. Optimal Control Strategy for a Discrete Time Smoking Model with Specific Saturated Incidence Rate, Hindawi, Discr. Dyn. Nat. Soc. 2018 (2018), Article ID 5949303.

[2] World Health Organization, Global health sector strategy against hepatitis 2016-2021 Jun 2016, https://apps.who.int/iris/bitstream/handle/10665/250577/WHO-HIV-2016.06-fre.pdf, Jun 2016.

[3] M. Lhous, M. Rachik, H. Laarabi, A. Abdelhak, Discrete mathematical modeling and optimal control of the marital status: the monogamous marriage case, Adv. Differ. Equ. 2017 (2017), 339

[4] S. Zhang, X. Xu, Dynamic analysis and optimal control for a model of hepatitis C with treatment, Commun. Nonlinear Sci. Numer. Simul. 46 (2017), 14–25.

[5] D.C. Zhang, B. Shi, Oscillation and global asymptotic stability in a discrete epidemic model, J. Math. Anal. Appl. 278 (2003), 194–202.

[6] C.L. Hwang, L.T. Fan, A discrete version of Pontryagin's maximum principle, Oper. Res. 15 (1967), 139–146.

[7] K. Abe, T. Kurata, T. Shikata, Non-A, non-B hepatitis: visualization of virus-like particles from chimpanzee and human sera, Arch. Virol. 104 (1989), 351–355.

[8] Communiqué de presse, Association de lutte contre le sida (ALCS), membre de Coalition PLUS, 30 mai 2018 à Casablanca, Maroc.

[9] https://www.who.int/fr/news-room/fact-sheets/detail/hepatitis-c.

[10] W. Ding, R. Hendon, B. Cathey, E. Lancaster, R. Germick, Discrete time optimal control applied to pest control problems, Involve. 7 (2014), 479–489.

[11] R.H. Westbrook, G. Dusheiko, Natural history of hepatitis C, J. Hepatol. 61 (2014), S58–S68.

[12] L.S. Pontryagin, V.G. Boltyanskii, R.V. Gamkrelidze, E.F. Mishchenko, The Mathematical Theory of Optimal Processes, JohnWiley and Sons, London, UK, 1962.

[13] K.O. Okosun, O.D. Makinde, Optimal control analysis of hepatitis C virus with acute and chronic stages in the presence of treatment and infected immigrants, Int. J. Biomath. 7

(2014), 1450019.

[14] lettre trimestrielle Pasteur Maroc, https:/www.pasteur.ma, Jan. 2016.

[15] World Health Organization.
https://www.who.int/fr/news-room/fact-sheets/detail/hepatitis-c, 9 Jul. 2019

[16] D. Lavanchy, Evolving epidemiology of hepatitis C virus, Clin. Microbiol. Infect. 17 (2011), 107–115.

[17] B. Hajarizadeh, J. Grebely, G.J. Dore, Epidemiology and natural history of HCV infection, Nat. Rev. Gastroenterol. Hepatol. 10 (2013), 553–562.

[18] World Health Organization.
https://www.who.int/fr/news-room/fact-sheets/detail/hepatitis-c, 9 jully 2019

[19] Global Burden of Disease and WHO/UNAIDS estimates, http://ihmeuw.org/3pmt (accessed 2 April 2016)

[20] WHO Global hepatitis report 2017.
https://apps.who.int/iris/bitstream/handle/10665/255016/9789241565455-eng.pdf, 2017.

[21] O. Zakary, M. Rachik, I. Elmouki, On the analysis of a multi-regions discrete SIR epidemic model: an optimal control approach, Int. J. Dynam. Control. 5 (2017), 917–930.

[22] A. Kouidere, A. Labzai, B. Khajji, et al. Optimal control strategy with multi-delay in state and control variables of a discrete mathematical modeling for the dynamics of diabetic population, Commun. Math. Biol. Neurosci. 2020 (2020), Article ID 14.

[23] A. Kouidere, O. Balatif, H. Ferjouchia, A. Boutayeb, M. Rachik, Optimal Control Strategy for a Discrete Time to the Dynamics of a Population of Diabetics with Highlighting the Impact of Living Environment, Discr. Dyn. Nat. Soc. 2019 (2019), Article ID 6342169.