Université Claude Bernard Lyon 1

The spread of STIs and HIV

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Abstract

In this paper, we model the evolution of human immunodeficiency virus and sexually transmitted infections incidences and the effect of a preventive treatment, pre-exposure prohylaxis, on both. To come with terms with this problem, we make use of different tools whether they are mathematical or numerical. Our study is mainly focused on recently designed models. The mathematical tools used in this paper are based on the theory of dynamical systems. First, we introduce the basic model of human immunodeficiency virus incidences without consideration of pre-exposure prohylaxis, then we include its prescription. Finally, we present an idea for a model that can further take into account the screenings induced by prescription of the preventive treatment.

Contents

1 Introduction

In the 1980s, the medical community encountered the first signs of what would become a major epidemic[1] [2]. The symptoms of acquired immune deficiency syndrome (AIDS) were first observed in the US amongst drug addicts and homosexuals but were shortly after encountered everywhere, in all communities[3]. It took a little over 10 years for researchers to come up with treatments such as the triple therapy which were able to effectively slow down the replication of human immunodeficiency virus (HIV), the virus responsible for AIDS, within the body. Thanks to these, it is now possible to live much longer whilst being contaminated than the original life expectancy. However, HIV keeps spreading and the epidemic is still a threat.

In 2007, scientists have come up with a new pill called Pre-Exposure Prophylaxis that is able to drastically slow down the spread of HIV. This pill is commonly referred to as PrEP. When taken appropriately, the treatment is very effective and the spread of HIV has noticeably decreased amongst the patients who receive a PrEP treatment[4]. Figure 1 below shows the decrease of HIV incidence with respect to PrEP intake.

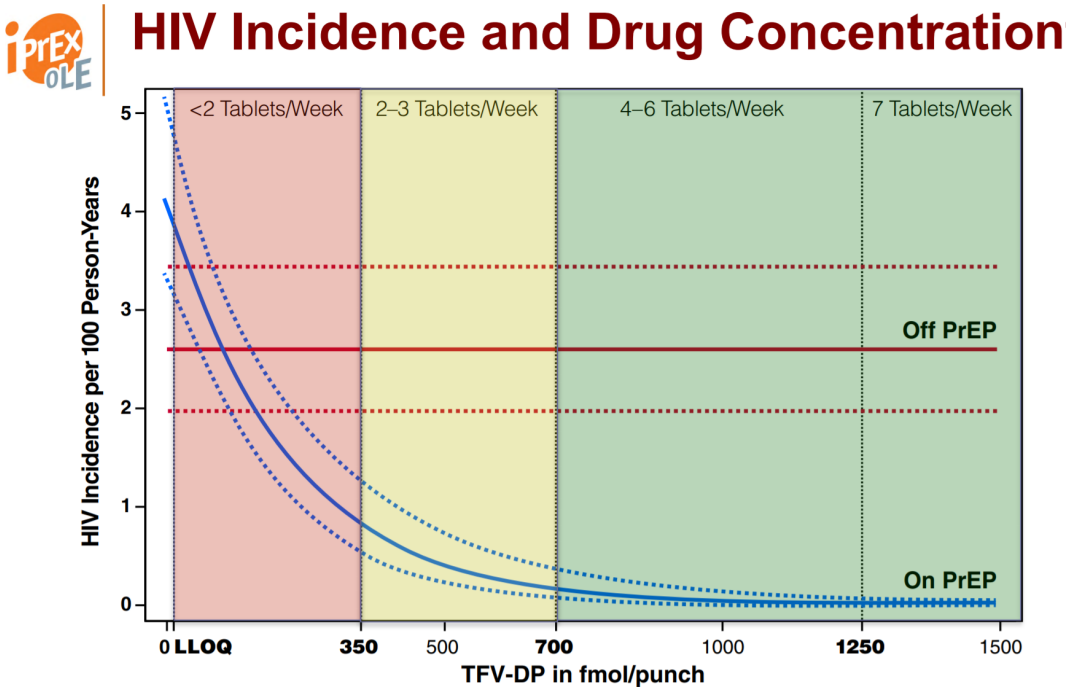

Figure 1: Evolution of HIV incidence with respect to PrEP intake[5]

However, it has been noticed that the spread of other sexually transmitted infections (STIs) amongst individuals receiving a PrEP treatment seemed greater than that of the

[1] https://www.inserm.fr/information-en-sante/dossiers-information/sida-et-vih
[2] https://cns.sante.fr/wp-content/uploads/2017/01/experts-vih_diversite.pdf
[3] https://www.avert.org/professionals/history-hiv-aids/overview
[4] http://www.anrs.fr/fr/presse/communiques-de-presse/518/1ers-resultats-de-letude-anrs-\prevenir-1-500-volontaires-0

rest of the population.[1] Bald assumptions can be made in that regard. When it comes to western countries, this can be linked with the fact that the drug is mostly prescribed to male homosexuals or to individuals working in the sex industry, since these populations present higher risks. Also, getting the treatment implies getting tested for all STIs much more frequently than average, which implies much more positive results.

The aim of this paper is to compare the spread of sexually transmitted infections amongst the patients treated with PrEP, to that spread of the non-treated population with the help of a model. Our goal is to answer the following questions : can we lower that spread by getting the patients tested more often? What would be the optimal interval between two tests? Can we find conditions where HIV and other STIs ultimately stop spreading at minimal costs?
In order to answer these questions, a first section is dedicated to introducing all the biological concepts needed in order to fully understand the model and its data. In a second section, we study the models that have already been designed regarding the spread of HIV and STIs. Finally, we introduce our own model which hopefully answers the above-mentioned questions. Ideally, our model eventually takes into account the underlying stochastic parameters.

2 Biological background

It is important to understand the difference between HIV/AIDS and STIs. HIV is the name of the virus responsible for AIDS, a chronic condition. No treatment has ever been found to permanently cure contaminated individuals. An STI (sexually transmitted infection) is an infection caused by a bacteria, virus or parasite that has been transmitted through sexual activity. For instance, AIDS is an STI caused by the HIV virus. Nowadays, most STIs such as chlamydia, gonorrhea or syphilis can be cured, apart from HIV/AIDS.

2.1 HIV

We recall that HIV stands for Human Immunodeficiency Virus. It is part of a subgroup of retroviruses, which means that it changes the genome of any cell that it has contaminated. More specifically, HIV is a lentivirus, meaning it has a long incubation period and eventually causes the death of contaminated cells. The stage at which HIV causes the death of contaminated cells is the final one of the contamination. This stage is usually called AIDS. HIV attacks white blood cells mostly, so an individual that has AIDS is severely immunodeficient, hence the acronym AIDS stands for Acquired Immune Deficiency Syndrome.
HIV-contaminated patients will usually follow a three-drug therapy, sometimes referred to as triple cocktail, which prevents severe immunodeficiency (AIDS) from happening.
On the other hand, there exists a form of prevention for uninfected individuals, called PrEP, which has proven itself to be very effective when taken appropriately.

2.2 Prevention

We observe different behaviours within the population at risk. Either they choose to take PrEP seriously and then become immune to HIV, or they prefer to use only condoms. One may wonder if people who choose to take PrEP cease using condoms, which makes them vulnerable to all the other STIs. On the other hand, people who choose to only use condoms are better protected from most STIs as long as no incident occur. Ideally, people would use both but the reality is far from it.

2.3 PrEP

Pre-exposure prophylaxis (or PrEP) is a treatment which prevents the infection from spreading. In France, individuals at higher risk of contamination can get a prescription for the PrEP treatment for a limited period of 3 months, and renew their prescription continuously until they consider not to be at risk anymore. Each time they renew their prescription, they get tested for a great number of STIs, including HIV of course. The idea behind this is to make sure to treat patients adequately if they do get infected, and to save money too. Indeed, it is 60% cheaper to treat people with PrEP than to treat

people with the triple cocktail therapy. For exemple, a box of PrEP-pills costs around 500 euros in France, which is the first country in the world that fully reimburses such a treatment. [6] [7] [8] [9]

2.4 Other STIs

There exists many different sexually transmitted infections, each of them causing more or less damage. Without regard of their threat potential, we will introduce the three most common STIs. For the well-being of readers, no picture will appear within the text.

2.4.1 Syphilis

Syphilis is the name given to the Treponema pallidum bacteria. It spreads through sexual mucous contact with someone who has it. It leads to the apparition of sores which are called chancres. When detected early and treated rapidly, syphilis has no serious effect. A lot of cases are asymptomatic in the early stage of the disease. On the other hand, untreated syphilis may lead to serious damage of the brain and impact cognitive abilities. As Syphilis creates lesions, infected people are more exposed to HIV. Reciprocally, as the immune system of HIV infected people is weaker, syphilis may progress much faster. The treatment for syphilis is in the form of a single intramuscular injection of penicillin. [10] [11]. Moreover, patients are advised not to have any sexual intercourse during the first seven days following the treatment.

2.4.2 Chlamydia

Chlamydia is another common bacterial STI which can be easily cured by antibiotics. The infection is carried in semen (cum), pre-cum, and vaginal fluids. As other STIs, it has no serious impact on health when detected and treated early but can lead to serious health problems if it remains untreated. As for the treatment of syphilis, the treatment of chalmydia is a single intramuscular injection of antibiotics, and again, no sexual intercourse is advised in the seven days following the injection. [12]

[6] http://prep-info.fr/wp-content/uploads/2016/04/GUIDE-PrEP_web.pdf
[7] http://www.infectiologie.com/UserFiles/File/formation/ecn-pilly-2018/ecn-2018-ue6-158-nb.pdf
[8] https://www.apmnews.com/freestory/0/301228/prep-au-vih-la-meta-analyse-suggerant-un-risque\-tres-eleve-d-ist-contestee
[9] https://www.sciencesetavenir.fr/sante/vih-la-tritherapie-permet-de-vivre-plus-vieux-a-\condition-d-etre-depiste-a-temps_112860
[10] https://www.nejm.org/doi/full/10.1056/NEJMoa044284
[11] https://www.catie.ca/fr/feuillets-info/infections/syphilis
[12] https://www.plannedparenthood.org/learn/stds-hiv-safer-sex

2.4.3 Gonorrhea

Gonorrhea is a sexually transmitted infection caused by the following bacteria : Neisseria Gonorrhea. In many cases, the infection is asymptomatic which is why regular screenings are recommended. Again, treatment for gonorrhea consists of a single intramuscular injection of antibiotics.

2.5 Epidemiological definitions

2.5.1 Basic reproduction number.

Later on in this paper, we will see that each model corresponding to a disease (HIV here) is linked to a number denoted by $\mathcal{R}_0$, called the basic reproduction number. The basic reproduction number of an infection is an indicator of the number of individuals a single infected one can transmit the pathogen of interest to. If this number is greater than 1, the disease will spread through the population. In the other case, the infection will eventually disappear.
Given its value, the evolution of the disease may change totally. It is an interesting indicator for public health authorities : in order to circumscribe the disease, public health measures may be voted. Indeed, we will see that $\mathcal{R}_0$ depends on certain parameters than humans have some power on.

2.5.2 Person-Time

Person-Time is an epidemiological notion which estimates the actual time-at-risk in years, months or days that all persons contributed to a study. [13]
For example, if 67 persons contributed to a study of 100 days, it will count as 6700 Person-days.
It allows us to define the rate as the number of new cases of disease during a period of time divided by the person-time-at-risk.

$$\text{rate} = \frac{\text{number of new cases}}{\text{total person-time at risk}}$$

3 Transition

In the following section, we present the results that are given in previous papers and articles such as Modeling and Optimal Control of HIV/AIDS Prevention Through PrEP by Silva and Torres, and Mathematical modeling and study of the impact of PrEP on STIs development by Thomas Martin.
Martin's paper extends the research and the results of Silva and Torres. We use the same

[13] https://sph.unc.edu/files/2015/07/nciph_ERIC4.pdf

notations as theirs so that consistency is assured. Their aim was to design a model able to explain the dynamical evolution between relevant categories of people.

4 HIV model without PrEP

Let us introduce the four groups of individuals that are considered in this study.

- **S(t)** Susceptible : Individuals that are not contaminated by HIV and thus haven't developed AIDS and do not follow the triple therapy.
- **I(t)** Infected : the infected people who are not treated and therefor can transmit the virus at a high rate.
- **A(t)** Infected people who also suffer from AIDS. They transmit the virus at an optimal rate.
- **C(t)** Infected people under antiviral triple therapy. They transmit the virus at a relatively low rate.

These four groups of individuals sum up to the total population denoted by N(t) at each instant of time. The goal is to construct a model that describes the evolution of each category with respect to time.

4.1 Model

In order to construct such a model, it is essential to describe how people move from one category to another.

- People from all category die naturally at rate μ
- Infected people develop AIDS at rate ρ : $I \xrightarrow{\rho} A$
- People suffering from AIDS are treated for AIDS (and therefor returning to category I) at rate α : $A \xrightarrow{\alpha} I$
- Infected people take ART treatment and move to the C category at rate ϕ : $I \xrightarrow{\phi} C$
- People under ART treatment stop the treatment at rate ω : $C \xrightarrow{\omega} I$
- Susceptible people are infected at rate $\lambda = S(t)\beta(I(t) + \eta_C C(t) + \eta_A A(t))/N(t)$ where β is the contact rate with HIV-infected individuals : $S \xrightarrow{\lambda} I$

Other facts about transmission need to be accounted for :

- People under ART are less infectious. The transmission rate of this category will therefore be multiplied by a coefficient $\eta_C \leq 1$
- People with AIDS are more infectious. The transmission rate of this category will therefore be multiplied by a coefficient $\eta_A \geq 1$

The methods used to calculate these coefficients will be developed in the section dedicated to statistics.
We illustrate the underlying system in the form of a diagram on figure 2 where the arrows represent the dynamics between each categories.

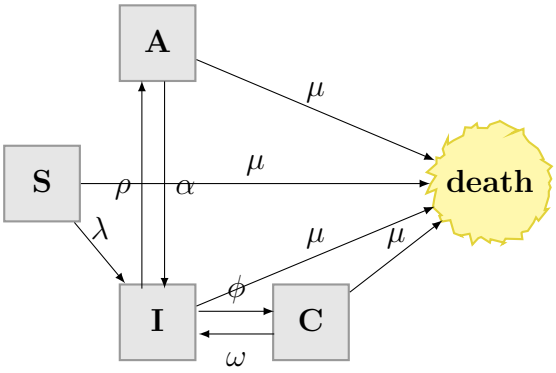

Figure 2: Evolution of the population in terms of HIV infection

We obtain the following system of equations defined for all $t \in I$, $I \subset \mathbb{R}_+$:

$$\begin{cases} \dot{S}(t) = \Lambda - \frac{\beta(I(t)+\eta_C C(t)+\eta_A A(t))}{N(t)} S(t) - \mu S(t) \\ \dot{I}(t) = \frac{\beta(I(t)+\eta_C C(t)+\eta_A A(t))}{N(t)} S(t) - (\rho + \phi + \mu) I(t) + \alpha A(t) + \omega C(t) \\ \dot{C}(t) = \phi I(t) - (\omega + \mu) C(t) \\ \dot{A}(t) = \rho I(t) - (\alpha + \mu + d) A(t) \end{cases} \tag{1}$$

Theorem (Well posedness of the system (1)). *For all t in $[0, t_f]$ and for all initial condition $(S(0), I(0), C(0), A(0)) \in \mathbb{R}_+^* \times \mathbb{R}_+^3$ there is one and only one solution $\mathcal{C}^1$. Moreover, $(S(t), I(t), C(t), A(t)) \in \mathbb{R}_+^* \times \mathbb{R}_+^3$ for all $t \in [0, t_f]$, $t_f \in \mathbb{R}_+$.*

Proof : We let $X(t) = (S(t), I(t), C(t), A(t))^T$, $X(t) \in \mathbb{R}^4$ and $t \in [0, t_f]$. Martin's proof is based on the Cauchy-Lipschitz theorem, which means that we want to find a continuous function $f : \mathbb{R}^5 \to \mathbb{R}^4$ such that $X'(t) = f(t, X(t))$ which is at least locally Lipschitz-continuous with respect to $X(t)$. Now let $f(t, X(t))$ be the following function :

$$f(t, X(t)) =$$
$$\begin{bmatrix} \Lambda - \frac{\beta(I(t)+\eta_C C(t)+\eta_A A(t))S(t)}{N(t)} \\ \frac{\beta(I(t)+\eta_C C(t)+\eta_A A(t))S(t)}{N(t)} \\ 0 \\ 0 \end{bmatrix} + \begin{bmatrix} -\mu & 0 & 0 & 0 \\ 0 & -(\rho + \phi_\mu) & \omega & \alpha \\ 0 & \phi & -(\omega + \mu) & 0 \\ 0 & \rho & 0 & -(\alpha + \mu + d) \end{bmatrix} \cdot X(t)$$

It is straight-forward to check that $X'(t) = f(t, X(t))$ as in equation (1). Moreover, f is a continuous function and so is its derivative. Thus, f is of class $\mathcal{C}^1$. Since we have defined it on a compact set, then we can conclude that f is Lipschitz continuous on this

set. Thus we can apply the Cauchy-Lipschitz theorem and conclude that there exists a unique solution $X(t)$ of class $\mathcal{C}^1$ and even $\mathcal{C}^2$ since $X'(t) = f(t, X(t))$ where f is of class $\mathcal{C}^1$.

4.2 Disease free equilibrium and basic reproduction number : Is it possible to reach an equilibrium where HIV is no more ?

We are interested in finding an equilibrium such that all the groups of HIV-infected people is equal to zero, meaning that the virus has been eliminated. Naturally, we would like such an equilibrium to be stable so that small perturbations don't result in catastrophes where the virus comes back.

Definition of a disease free equilibrium The disease free equilibrium is a point $(S^0, I^0, C^0, A^0) \in \mathbb{R}_+^* \times \mathbb{R}_+^3$ satisfying the system of equations (1), such that $(I^0, C^0, A^0) = (0, 0, 0)$ and $(\dot{S}^0(t), \dot{I}^0(t), \dot{C}^0(t), \dot{A}^0(t)) = (0, 0, 0, 0)$.

Theorem (Uniqueness)**.** *There is only one disease free equilibrium.*

Proof : Instead of an analytical proof, we show that the disease-free equilibrium is unique by construction.
We now compute this equilibrium. Using the condition that $(\dot{S}^0(t), \dot{I}^0(t), \dot{C}^0(t), \dot{A}^0(t)) = (0, 0, 0, 0)$, we have :

$$\begin{bmatrix} \Lambda - \frac{\beta(I^0(t)+\eta_C C^0(t)+\eta_A A^0(t))}{N(t)} S^0(t) - \mu S^0(t) \\ \frac{\beta(I^0(t)+\eta_C C^0(t)+\eta_A A^0(t))}{N(t)} S^0(t) - (\rho + \phi + \mu) I^0(t) + \alpha A^0(t) + \omega C^0(t) \\ \phi I^0(t) - (\omega + \mu) C^0(t) \\ \rho I^0(t) - (\alpha + \mu + d) A^0(t) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

Now forcing the condition that $(I^0(t), C^0(t), A^0(t)) = (0, 0, 0)$, we get :

$$\begin{bmatrix} \Lambda - \mu S^0(t) \\ 0 \\ 0 \\ 0 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \iff \begin{bmatrix} S^0(t) \\ 0 \\ 0 \\ 0 \end{bmatrix} = \begin{bmatrix} \frac{\Lambda}{\mu} \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

Thus, the unique disease free equilibrium is

$$\Sigma_0 = (S^0, I^0, C^0, A^0) = (\frac{\Lambda}{\mu}, 0, 0, 0)$$

4.3 Basic reproduction number

We compute the basic reproduction number following the method described by P.van den Driessche and James Watmough in their article on "Reproduction numbers and subthreshold endemic equilibria for compartmental models of disease transmission" [2].
In order to compute R_0 we only consider the number of people in the infected compartments : I, C and A.

We define the following functions :

- F rate of appearance of new infection in a given compartment
- V^+ rate of transfer of individuals into a given compartment by all other means
- V^- rate of transfer out of a given compartment

We define then $V = V^- - V^+$.
F and V are functions of the variables I, C and A.

$$F = \begin{pmatrix} \frac{\beta(I(t)+\eta_C C(t)+\eta_A A(t))}{N(t)} S(t) \\ 0 \\ 0 \end{pmatrix}, \; V = \begin{pmatrix} (\rho+\phi+\mu)I(t) - \alpha A(t) - \omega C(t) \\ -\phi I(t) + (\omega+\mu)C(t) \\ -\rho I(t) + (\alpha+\mu+d)A(t) \end{pmatrix}$$

We then compute the Jacobian matrices of these functions evaluated at the equilibrium.

$$\mathcal{F} = \begin{pmatrix} \frac{\beta S^0}{N^0} & \frac{\beta \eta_C S^0}{N^0} & \frac{\beta \eta_A S^0}{N^0} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \; \mathcal{V} = \begin{pmatrix} (\rho+\phi+\mu)I & -\omega & -\alpha \\ -\phi & (\omega+\mu) & 0 \\ -\rho & 0 & (\alpha+\mu+d) \end{pmatrix}$$

We now make use of the following theorem from van den Driessche and Watmough's article :

Theorem. *The matrix $\mathcal{V}$ is nondegenerate and the basic reproduction number $\mathcal{R}_0$ is given by the greatest non-negative real eigenvalue of $\mathcal{F}\mathcal{V}^{-1}$.*

We will compute the inverse of $\mathcal{V}$ with the formula : $\mathcal{V}^{-1} = \frac{1}{\det(\mathcal{V})} {}^t\mathrm{com}(\mathcal{V})$

$$\begin{aligned} \det(\mathcal{V}) &= -\rho \begin{vmatrix} -\omega & -\alpha \\ (\omega+\mu) & 0 \end{vmatrix} + (\alpha+\mu+d) \begin{vmatrix} (\rho+\phi+\mu) & -\omega \\ -\phi & (\omega+\mu) \end{vmatrix} \\ &= -\rho\alpha(\omega+\mu) + (\alpha+\mu+d)(\rho+\phi+\mu)(\omega+\mu) - \omega\phi(\alpha+\mu+d) \end{aligned}$$

$$\text{com}(\mathcal{V}) = \begin{pmatrix} (\omega+\mu)(\alpha+\mu+d) & \phi(\alpha+\mu+d) & \rho(\omega+\mu) \\ \omega(\alpha+\mu+d) & (\alpha+\mu+d)(\rho+\phi+\mu)-\alpha\rho & \omega\rho \\ \alpha(\omega+\mu) & \alpha\phi & (\omega+\mu)(\rho+\phi+\mu)-\omega\phi \end{pmatrix}$$

The first row of $\mathcal{F}$ is the only non-zero one, thus the shape of $\mathcal{F}\mathcal{V}^{-1}$ is $\begin{pmatrix} \mathcal{R}_0 & * & * \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$.
This allows us to find the greatest eigenvalue $\mathcal{R}_0$ right away.

$$\mathcal{R}_0 = \frac{1}{N^0 \det(\mathcal{V})}\Big((\beta S^0(\omega+\mu)(\alpha+\mu+d) + \beta\eta_C S^0\omega(\alpha+\mu+d) + \beta\eta_A S^0(\omega+\mu)\alpha\Big)$$

Let $\xi_1 = \alpha+\mu+d$, $\xi_2 = \omega+\mu$ and $\xi_3 = \rho+\phi+\mu$. This gives us the following :

$$\mathcal{R}_0 = \frac{\beta(\xi_2(\xi_1+\rho\eta_A)+\eta_C\phi\xi_1)}{\mu(\xi_2(\rho+\xi_1)+\phi\xi_1+\rho d)+\rho\omega d} = \frac{\mathcal{N}}{\mathcal{D}}$$

by definition of $\mathcal{N}$ and $\mathcal{D}$.

Remark The stability of an equilibrium is given by R_0. R_0 depends on the initial parameters of the system.

Theorem. *The disease free equilibrium Σ_0 is globally asymptotically stable for $R_0 < 1$.*

Proof Let $X(t) = [S(t), I(t), C(t), A(t)]$. The model is equivalent to $\dot{X}(t) = \varphi(X(t))$, where :

$$\varphi(X(t)) = \begin{bmatrix} \Lambda - \frac{\beta(I(t)+\eta_C C(t)+\eta_A A(t))}{N(t)} S(t) - \mu S(t) \\ \frac{\beta(I(t)+\eta_C C(t)+\eta_A A(t))}{N(t)} S(t) - (\rho+\phi+\mu)I(t) + \alpha A(t) + \omega C(t) \\ = \phi I(t) - (\omega+\mu)C(t) \\ = \rho I(t) - (\alpha+\mu+d)A(t) \end{bmatrix}$$

Now let $\tilde{\varphi}(X(t)) = \varphi(\Sigma_0 - X(t))$. Then the origin is an equilibrium point for $\tilde{\varphi}$. We have :

$$\tilde{\varphi}(X(t)) = \begin{bmatrix} \frac{\beta(I(t)+\eta_C C(t)+\eta_A A(t))}{N(t)}(\frac{\Lambda}{\mu} - S(t)) + \mu S(t) \\ -\frac{\beta(I(t)+\eta_C C(t)+\eta_A A(t))}{N(t)}(\frac{\Lambda}{\mu} - S(t)) + (\rho+\phi+\mu)I(t) - \alpha A(t) - \omega C(t) \\ -\phi I(t) + (\omega+\mu)C(t) \\ -\rho I(t) + (\alpha+\mu+d)A(t) \end{bmatrix}$$

$$= \begin{bmatrix} \frac{\beta(I(t)+\eta_C C(t)+\eta_A A(t))}{N(t)}(\frac{\Lambda}{\mu} - S(t)) + \mu S(t) \\ -\frac{\beta(I(t)+\eta_C C(t)+\eta_A A(t))}{N(t)}(\frac{\Lambda}{\mu} - S(t)) + \xi_3 I(t) - \alpha A(t) - \omega C(t) \\ -\phi I(t) + \xi_2 C(t) \\ -\rho I(t) + \xi_1 A(t) \end{bmatrix}$$

Let us consider the following function :

$$L = (\xi_1\xi_2+\xi_1\phi\eta_C+\xi_2\rho\eta_A)I+(\xi_1\omega+\xi_1\xi_3\eta_C+\rho\eta_A\omega-\eta_C\rho\alpha)C+(\alpha\xi_2+\xi_2\xi_3\eta_A+\phi\eta_C\alpha-\phi\eta_A\omega)A$$

This function is nonnegative for all positive t because all the parameters are nonnegatives and $\frac{\eta_A}{\alpha} \geq \frac{\eta_C}{\omega}$ according to the estimated values. This function is equal to 0 only whenever I, C and A are null, so in particular at the disease free equilibrium. Then L is a Lyapunov function associated to the function $\tilde{\varphi}$. Now, we are interested in the variations of L with respect to time :

$$\dot{L} = (\xi_1\xi_2+\xi_1\phi\eta_C+\xi_2\rho\eta_A)\dot{I}+(\xi_1\omega+\xi_1\xi_3\eta_C+\rho\eta_A\omega-\eta_C\rho\alpha)\dot{C}+(\alpha\xi_2+\xi_2\xi_3\eta_A+\phi\eta_C\alpha-\phi\eta_A\omega)\dot{A}$$

Thanks to Martin's calculation in his paper [3], we know the following :

$$\begin{aligned} \dot{L} &= \mathcal{D}(\mathcal{R}_0\frac{S}{N} - 1)I + \eta_C\mathcal{D}(\mathcal{R}_0\frac{S}{N} - 1)C + \eta_A\mathcal{D}(\mathcal{R}_0\frac{S}{N} - 1)A \\ &\leq \mathcal{D}(\mathcal{R}_0 - 1)I + \eta_C\mathcal{D}(\mathcal{R}_0 - 1)C + \eta_A\mathcal{D}(\mathcal{R}_0 - 1)A \\ &\leq 0 \text{ for } \mathcal{R}_0 < 1 \end{aligned}$$

Thus, using the Lyapunov Theorem, we conclude that the origin is an asymptotically stable equilibrium of $\tilde{\varphi}$ for $\mathcal{R}_0 < 1$ and by translation of $\tilde{\varphi}$, that the disease-free equilibrium of φ is asymptotically stable.

4.4 Study of the endemic equilibrium : When will the disease set in the population ?

At some point, the disease may stop spreading in the population and remain stable but not null. In this case, the evolution has reached what can be called an endemic equilibrium. We are interested in finding these equilibrium. Indeed, analyzing such unwanted equilibrium might allow us to construct regions and conditions to set ourselves in, so that we avoid converging towards these points.

Definition of an endemic equilibrium The endemic equilibrium is a point $(S^*, I^*, C^*, A^*) \in \mathbb{R}_+^* \times \mathbb{R}_+^3$ satisfying the system of equations (1), such that $I^* > 0$ or $C^* > 0$ or $A^* > 0$, and $(\dot{S^*}(t), \dot{I^*}(t), \dot{C^*}(t), \dot{A^*}(t)) = (0, 0, 0, 0)$.

By construction again, we will show that such an equilibrium is unique in our system.

Resolution Let $(S^*, I^*, C^*, A^*) \in \mathbb{R}_+^* \times \mathbb{R}_+^3$ be an endemic equilibrium of the system.

$$\begin{cases} 0 = \Lambda - \frac{\beta(I^* + \eta_C C^* + \eta_A A^*)}{N^*} S^*) - \mu S^* \\ 0 = \frac{\beta(I^* + \eta_C C^* + \eta_A A^*)}{N^*} S^* - (\rho + \phi + \mu) I^* + \alpha A^* + \omega C^* \\ 0 = \phi I^* - (\omega + \mu) C^* \\ 0 = \rho I^* - (\alpha + \mu + d) A^* \end{cases} \tag{2}$$

Let

$$\lambda^* = \frac{\beta(I^* + \eta_C C^* + \eta_A A^*)}{N^*},$$
$$\xi_1 = \alpha + \mu + d, \xi_2 = \omega + \mu \text{and} \xi_3 = \rho + \Phi + \mu$$

The system is simplified as :

$$\begin{cases} 0 = \Lambda - \lambda^* S^*) - \mu S^* \\ 0 = \lambda^* S^* - (\rho + \phi + \mu) I^* + \alpha A^* + \omega C^* \\ 0 = \phi I^* - (\omega + \mu) C^* \\ 0 = \rho I^* - (\alpha + \mu + d) A^* \end{cases} \tag{3}$$

This system of 4 equations and 4 variables has a unique solution :

$$S^* = \frac{\Lambda}{\lambda^* + \mu}\ ,\ I^* = \frac{\lambda^* \Lambda \xi_1 \xi_2}{(\lambda^* + \mu)\mathcal{D}}\ ,$$
$$C^* = \frac{\Phi \lambda^* \Lambda \xi_1}{(\lambda^* + \mu)\mathcal{D}}\ ,\ A^* = \frac{\rho \lambda^* \Lambda \xi_2}{(\lambda^* + \mu)\mathcal{D}}$$

Theorem : *The endemic equilibrium is globally asimptotically stable whenever* $R_0 > 1$ *and the initial conditions are non zero.*

Proof : This proof can be found in Silva and Torres' article [4]

4.5 Numerical simulations

We wrote an algorithm on Scilab in order to plot possible trajectories of the SICA model. This code can be found in the annex. For that purpose, we used the explicit Euler method to solve our ODE. As initial values, we took the same ones as Martin, namely $S(0) = 323911$, $I(0) = 61$ and $C(0) = A(0) = 0$. We first use the following parameters, computed by Silva and Torres [4] :

Notation	Meaning	Value
$N(0)$	Initial population	323972 ind
Λ	Recruitment rate	$13045\text{ind.year}^{-1}$
μ	Natural death rate	$1/69.54\text{year}^{-1}$
β	HIV transmission rate	0.752year^{-1}
η_C	Modification parameter	0.04
η_A	Modification parameter	1.35
ϕ	HIV treatment rate for I individuals	1year^{-1}
ρ	Default treatment rate for I individuals	0.1year^{-1}
α	AIDS treatment rate	0.33year^{-1}
ω	Default treatment rate for C individuals	0.09year^{-1}
d	AIDS induced death rate	1year^{-1}

Moreover, these parameters are such that $\mathcal{R}_0 = 4.86$, which means that in the current situation, we do not expect HIV to disappear but on the other hand, the illness should set in until it reaches an equilibrium. Let's see the output of our simulations where figures 3, 4, 5 and 6 respectively show the evolutions of the susceptibles, the infected, the patients under ART treatment and the infected with AIDS with respect to time :

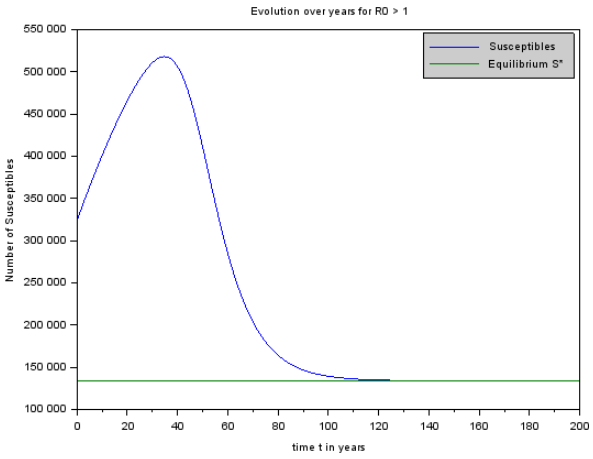

Figure 3: Evolution of S with respect to time when $\mathcal{R}_0 > 1$

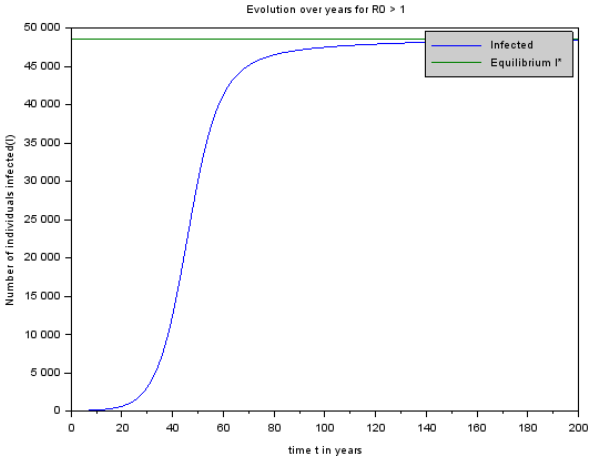

Figure 4: Evolution of I with respect to time when $\mathcal{R}_0 > 1$

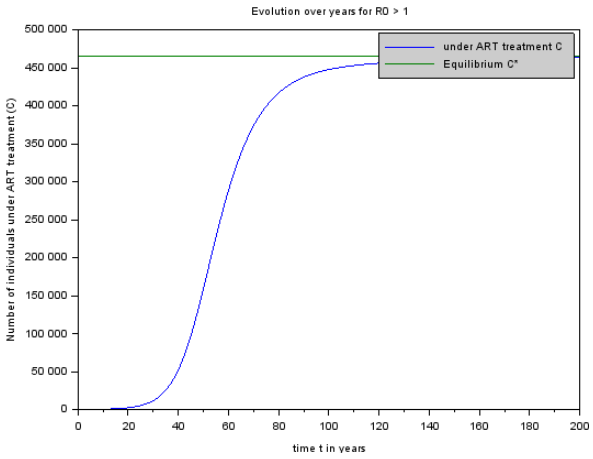

Figure 5: Evolution of C with respect to time when $\mathcal{R}_0 > 1$

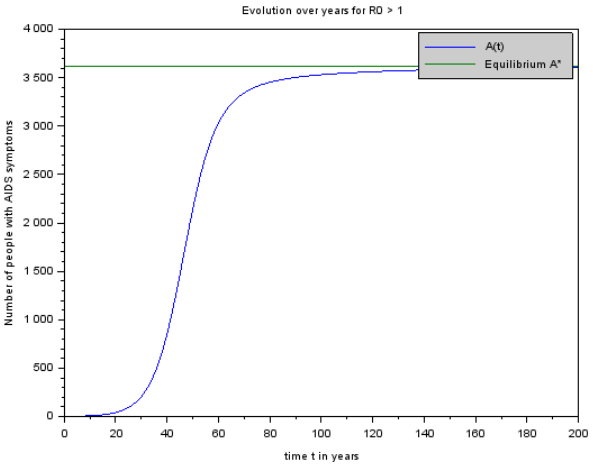

Figure 6: Evolution of A with respect to time $\mathcal{R}_0 > 1$

We see that the output is coincides with the analytical results. Indeed, since $\mathcal{R}_0 > 1$, we see that our population converges to the endemic equilibrium.

Now suppose that drastic measures have been taken and people start to and/or must use the condom massively. This would make the parameter β decrease a lot. On the numerical simulation shown on figures 7 and 8, we take $beta = 0.153$ which gives us $\mathcal{R}_0 = 0.99$. We assume that at the start, one third of the population is infected (one third of the population belongs to category I) but that $C(0) = A(0) = 0$. The reason for two figures of the same graph is to show both the short and the long term effects. Here are the outputs :

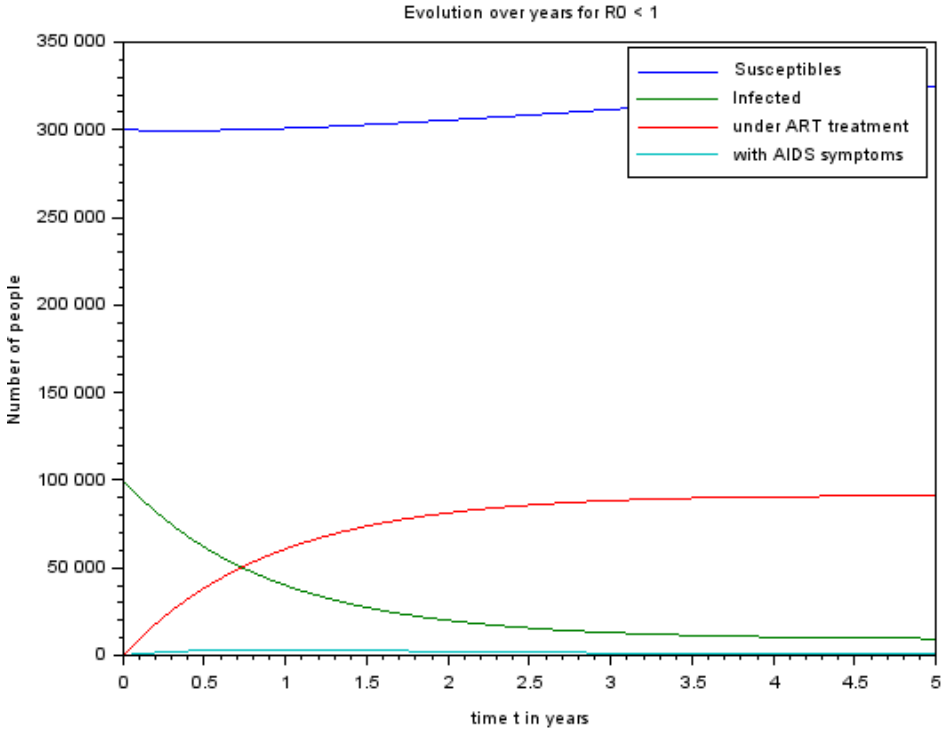

Figure 7: Evolution of each category in the short term when $R_0 < 1$

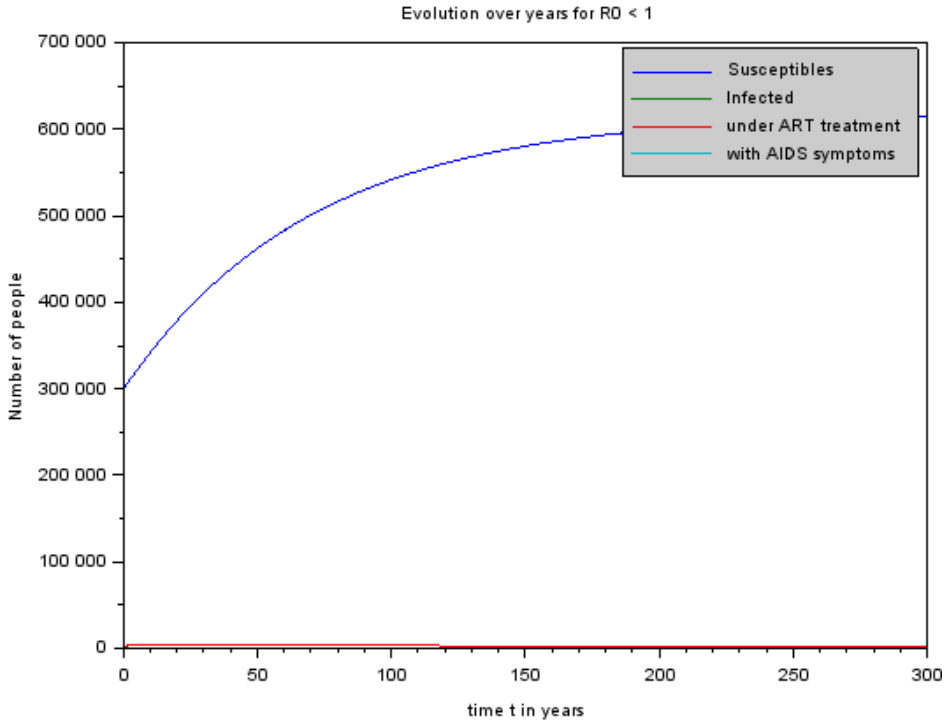

Figure 8: Evolution of each category in the long term when $\mathcal{R}_0 < 1$

We see that, indeed, in the very long term, our population converges to the expected disease-free equilibrium. However, it takes a lot of time (300 years) to reach that equilibrium. It would be interesting to see in further research which change of other parameters

would make the trajectory converge faster to a disease-free one.

5 HIV model with PrEP

5.1 Model

In this model, we take into account the group of people following a PrEP treatment. We denote by E(t) the amount of people in this category at each instant of time. Those people can only origin from the group of uninfected people, denoted by S. It is assumed that uninfected people chose to start a PrEP treatment at a rate ψ where $0 \leq \psi \leq 1$ and on the other hand, people who are treated chose to stop the treatment and move back to the group of susceptible individuals at a rate θ, where $0 \leq \theta \leq 1$. The new model has all the properties of the first one, with the added constraints mentioned above. Thus, it leads to the following system of ordinary differential equations defined for all $t \in I$, $I \subset \mathbb{R}_+$:

$$\begin{cases} \dot{S}(t) = \Lambda - \frac{\beta(I(t)+\eta_C C(t)+\eta_A A(t))}{N(t)} S(t) - (\mu+\psi)S(t) + \theta E(t) \\ \dot{I}(t) = \frac{\beta(I(t)+\eta_C C(t)+\eta_A A(t))}{N(t)} S(t) - (\rho+\phi+\mu)I(t) + \alpha A(t) + \omega C(t) \\ \dot{C}(t) = \phi I(t) - (\omega+\mu)C(t) \\ \dot{A}(t) = \rho I(t) - (\alpha+\mu+d)A(t) \\ \dot{E}(t) = \psi S(t) - (\theta+\mu)E(t) \end{cases} \tag{4}$$

where figure 9 gives a visual representation of the dynamics between each category of people :

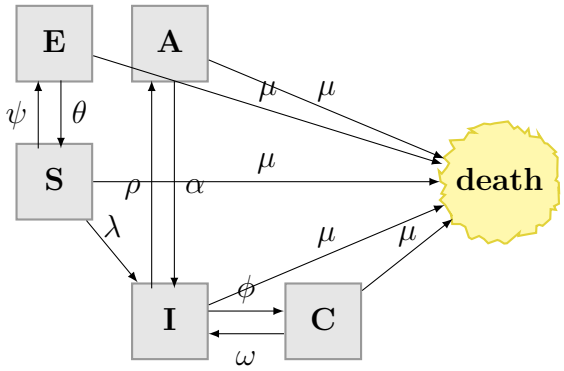

Figure 9: Evolution of the population in terms of HIV infection

Theorem (Well posedness of the system (4)). *For all t in $[0, t_f]$ and for all initial conditions*
$(S(0), I(0), C(0), A(0), E(0)) \in \mathbb{R}_+^* \times \mathbb{R}_+^4$ *there is one and only one solution* $\mathcal{C}^1$ *(even* $\mathcal{C}^\infty$*). Moreover,* $(S(t), I(t), C(t), A(t), E(t)) \in \mathbb{R}_+^* \times \mathbb{R}_+^4$ *for all* $t \in [0, t_f]$

Proof : The proof is analogous to the one for the SICA model above.

5.2 Disease-free equilibrium

We now compute the disease-free equilibrium, i.e. a point (S, I, C, A, E) such that $S, E \in \mathbb{R}_+^*$ and $I = C = A = 0$. Using the fact that $(\dot{S^0}(t), \dot{I^0}(t), \dot{C^0}(t), \dot{A^0}(t), (\dot{E^0}(t)) = (0, 0, 0, 0, 0)$, we have :

$$\begin{bmatrix} \Lambda - \frac{\beta(I(t)+\eta_C C(t)+\eta_A A(t))}{N(t)} S(t) - (\mu+\psi)S(t) + \theta E(t) \\ \frac{\beta(I(t)+\eta_C C(t)+\eta_A A(t))}{N(t)} S(t) - (\rho+\phi+\mu)I(t) + \alpha A(t) + \omega C(t) \\ \phi I(t) - (\omega+\mu)C(t) \\ \rho I(t) - (\alpha+\mu+d)A(t) \\ \psi S(t) - (\theta+\mu)E(t) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

Now forcing the condition that $(I^0(t), C^0(t), A^0(t)) = (0, 0, 0)$, we get :

$$\begin{bmatrix} \Lambda - (\mu+\psi)S(t) + \theta E(t) \\ \psi S(t) - (\theta+\mu)E(t) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix} \iff \begin{bmatrix} S^0(t) \\ E^0(t) \end{bmatrix} = \begin{bmatrix} \frac{(\theta+\mu)\Lambda}{\mu(\theta+\psi+\mu)} \\ \frac{\psi\Lambda}{\mu(\theta+\psi+\mu)} \end{bmatrix}$$

Thus, the unique disease free equilibrium is

$$\Sigma_0 = (S^0, I^0, C^0, A^0, E^0) = (\frac{(\theta+\mu)\Lambda}{\mu(\theta+\psi+\mu)}, 0, 0, 0, \frac{\psi\Lambda}{\mu(\theta+\psi+\mu)})$$

This is the unique disease free equilibrium because there is only one solution to this system with the constraints A=I=C=0 as a consequence of Cauchy-Lipschitz.

5.3 Basic reproduction number

In order to compute the basic reproduction number, we use the same method as above, in the model without PReP. The functions F, V^+ and V^- are defined in the same way. We recall :

- F rate of appearance of new infections in all compartments
- V^+ rate of transfer of individuals in o othet compartmbntsery all other means
- V^- rate of transfer out of the compartments

We define $V = V^- - V^+$. We get :

$$F = \begin{pmatrix} \frac{\beta(I(t)+\eta_C C(t)+\eta_A A(t))}{N(t)} S(t) \\ 0 \\ 0 \end{pmatrix}, \; V = \begin{pmatrix} (\rho+\phi+\mu)I(t) - \alpha A(t) - \omega C(t) \\ -\phi I(t) + (\omega+\mu)C(t) \\ -\rho I(t) + (\alpha+\mu+d)A(t) \end{pmatrix}$$

We then compute the Jacobian matrices of these functions evaluated at the disease-free equilibrium.

$$\mathcal{F} = \begin{pmatrix} \frac{\beta S^0}{N^0} & \frac{\beta \eta_C S^0}{N^0} & \frac{\beta \eta_A S^0}{N^0} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix} (\rho+\phi+\mu)I & -\omega & -\alpha \\ -\phi & (\omega+\mu) & 0 \\ -\rho & 0 & (\alpha+\mu+d) \end{pmatrix}$$

We recall and use one more time following theorem :

Theorem. *The matrix $\mathcal{V}$ is nondegenerate and the basic reproduction number $\mathcal{R}_0$ is given by the greatest non-negative real eigenvalue of $\mathcal{F}\mathcal{V}^{-1}$.*

The inverse of $\mathcal{V}$ is : $\mathcal{V}^{-1} = \frac{1}{\det(\mathcal{V})}{}^t\mathrm{com}(\mathcal{V})$, where :

$$\mathrm{com}(\mathcal{V}) = \begin{pmatrix} (\omega+\mu)(\alpha+\mu+d) & \phi(\alpha+\mu+d) & \rho(\omega+\mu) \\ \omega(\alpha+\mu+d) & (\alpha+\mu+d)(\rho+\phi+\mu)-\alpha\rho & \omega\rho \\ \alpha(\omega+\mu) & \alpha\phi & (\omega+\mu)(\rho+\phi+\mu)-\omega\phi \end{pmatrix}$$

and

$$\begin{aligned} \det(\mathcal{V}) &= -\rho \begin{vmatrix} -\omega & -\alpha \\ (\omega+\mu) & 0 \end{vmatrix} + (\alpha+\mu+d) \begin{vmatrix} (\rho+\phi+\mu) & -\omega \\ -\phi & (\omega+\mu) \end{vmatrix} \\ &= -\rho\alpha(\omega+\mu) + (\alpha+\mu+d)(\rho+\phi+\mu)(\omega+\mu) - \omega\phi(\alpha+\mu+d) \end{aligned}$$

Again, we notice that $\mathcal{F}\mathcal{V}^{-1}$ only has non-zero components on its first row. Thus, we are able to draw the same conclusion as above, namely that the greatest eigenvalue of $\mathcal{F}\mathcal{V}^{-1}$ is equal to the value on its first row and column, and we know that this value is R_0. In order to distinguish the R_0 of the model with PrEP to that of the model without PrEP, we denote the new $\mathcal{R}_0$ by $\tilde{\mathcal{R}}_0$. We have :

$$\begin{aligned} \tilde{\mathcal{R}}_0 &= \frac{1}{N^0\det(\mathcal{V})}\left(\beta S^0(\omega+\mu)(\alpha+\mu+d) + \beta\eta_C S^0\omega(\alpha+\mu+d) + \beta\eta_A S^0(\omega+\mu)\alpha\right) \\ &= \frac{\beta S^0(\omega+\mu)(\alpha+\mu+d) + \beta\eta_C S^0\omega(\alpha+\mu+d) + \beta\eta_A S^0(\omega+\mu)\alpha}{(S^0+E^0)\det(\mathcal{V})} \\ &= \frac{\beta(\theta+\mu)(\xi_2(\xi_1+\rho\eta_A)+\eta_C\phi\xi_1)}{(\theta+\psi+\mu)(\mu(\xi_2(\rho+\xi_1)+\phi\xi_1+\rho d)+\rho\omega d)} \\ &= \frac{(\theta+\mu)\mathcal{N}}{(\theta+\psi+\mu)\mathcal{D}} = \frac{\theta+\mu}{\theta+\mu+\psi}\mathcal{R}_0 \end{aligned}$$

Theorem. *The disease free equilibrium Σ_0 is globally asymptotically stable for $R_0 < 1$.*

Proof We assume the following :

- AIDS induced mortality is negligible so we force the condition $d = 0$
- On the short term, the global population remains constant which means that $N = \frac{\Lambda}{\mu}$
- People under PrEP comply with the prescription which means that $\theta = 0$

Let us consider the following function :

$$L = (\xi_1\xi_2 + \xi_1\phi\eta_C + \xi_2\rho\eta_A)(S - S^0 ln(S)) - (S^0 - S^0 ln(S^0)) + (\xi_1\xi_2 + \xi_1\phi\eta_C + \xi_2\rho\eta_A)I$$

$$+(\xi_1\omega + \xi_1\xi_3\eta_C + \rho\eta_A\omega - \eta_C\rho\alpha)C + (\alpha\xi_2 + \xi_2\xi_3\eta_A + \phi\eta_C\alpha - \phi\eta_A\omega)A$$

This function is nonnegative for all positive t and zero only when $(S, I, C, A) = (S^0, 0, 0, 0)$. Now, let us compute the time derivative of L :

$$\dot{L} = (\xi_1\xi_2 + \xi_1\phi\eta_C + \xi_2\rho\eta_A)(1 - \frac{S_0}{S})\dot{S} + (\xi_1\xi_2 + \xi_1\phi\eta_C + \xi_2\rho\eta_A)\dot{I} + (\xi_1\omega + \xi_1\xi_3\eta_C + \rho\eta_A\omega - \eta_C\rho\alpha)\dot{C}$$
$$+ (\alpha\xi_2 + \xi_2\xi_3\eta_A + \phi\eta_C\alpha - \phi\eta_A\omega)\dot{A}$$

When replacing each derivative S, I, C and A by their explicit value and after using the relation $\Lambda = (\mu + \psi)S_0$, we get :

$$\dot{L} = (1 - \frac{S_0}{S})(S_0 - S)(\mu + \psi) + \mathcal{D}(\tilde{\mathcal{R}}_0 - 1)I + \eta_C\mathcal{D}(\tilde{\mathcal{R}}_0 - 1)C + \eta_A\mathcal{D}(\tilde{\mathcal{R}}_0 - 1)A$$

and, from this expression, we see clearly that $\dot{L} < 0$ whenever $\tilde{\mathcal{R}}_0 < 1$.

Thus, using the Lyapunov Theorem, we conclude that the disease-free equilibrium of φ is asymptotically stable.

5.4 Numerical simulations

The code can be found in the annex. We used the explicit Euler method to solve our ODE. As initial values, we took the same ones as Martin, namely $S(0) = 323911$, $I(0) = 61$ $C(0) = A(0) = 0$ and $E(0) = 5$. We first use the following parameters :

Notation	Meaning	Value
$N(0)$	Initial population	323972 ind
Λ	Recruitment rate	$13045\text{ind.year}^{-1}$
μ	Natural death rate	$1/69.54\text{year}^{-1}$
β	HIV transmission rate	0.1year^{-1}
η_C	Modification parameter	0.04
η_A	Modification parameter	1.35
ϕ	HIV treatment rate for I individuals	1year^{-1}
ψ	rate of PrEP treatment rate for S individuals	0.1year^{-1}
ρ	Default treatment rate for I individuals	0.1year^{-1}
α	AIDS treatment rate	0.33year^{-1}
ω	Default treatment rate for C individuals	0.09year^{-1}
d	AIDS induced death rate	0.2year^{-1}

Moreover, these parameters are such that $\mathcal{R}_0 = 0.19$, which means that HIV is doomed to disappear. Let's see the output of our simulations where figures 10, 11, 12, 13 and 14 respectively show the evolutions of the susceptibles, the infected, the patients under ART treatment and the infected with AIDS with respect to time :

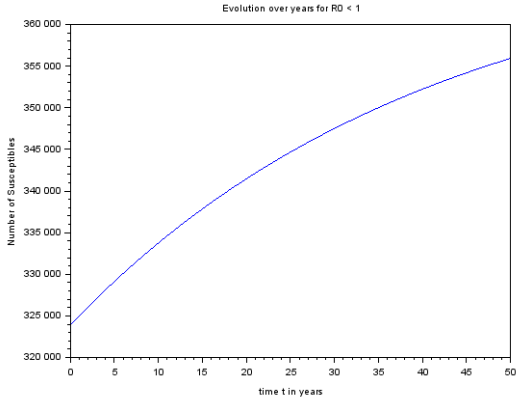

Figure 10: Evolution of S with respect to time when $\mathcal{R}_0 < 1$

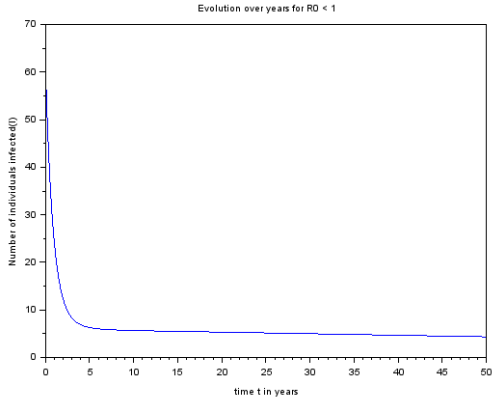

Figure 11: Evolution of I with respect to time when $\mathcal{R}_0 < 1$

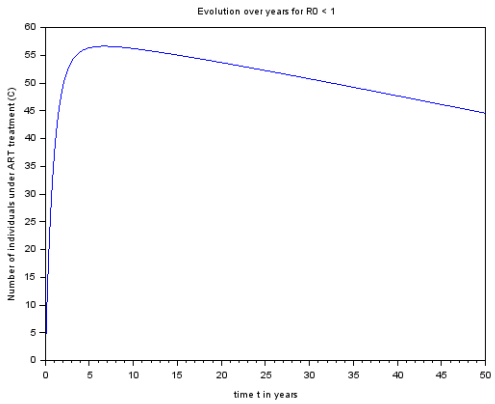

Figure 12: Evolution of C with respect to time when $\mathcal{R}_0 < 1$

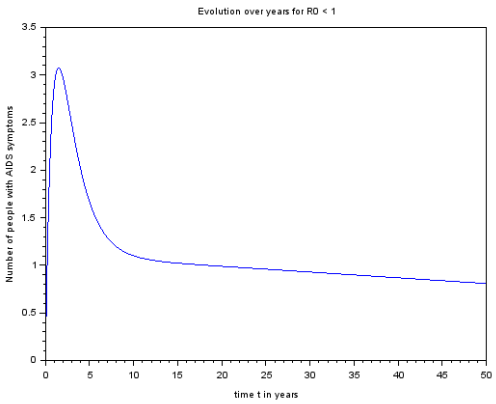

Figure 13: Evolution of A with respect to time when $\mathcal{R}_0 < 1$

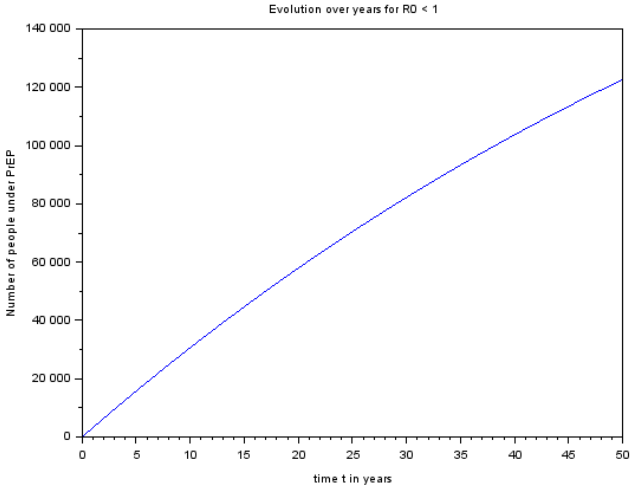

Figure 14: Evolution of E with respect to time when $\mathcal{R}_0 < 1$

The numerical simulations confirm that whenever $\mathcal{R}_0 < 1$, the trajectories reaches a disease-free equilibrium.

5.5 Study of the endemic equilibrium

First, we make the same assumptions as above, that greatly simplify the model :

- $d = 0$ We assume that AIDS induced no death
- N is constant
- $\theta = 0$ We assume that people stick to their treatment

Let's rewrite the model with PrEP, taking into account our assumptions :

$$\begin{cases} \dot{S}(t) = \Lambda - \frac{\beta(I(t)+\eta_C C(t)+\eta_A A(t))}{N} S(t) - (\mu+\psi)S(t) \\ \dot{I}(t) = \frac{\beta(I(t)+\eta_C C(t)+\eta_A A(t))}{N} S(t) - \xi_3 I(t) + \alpha A(t) + \omega C(t) \\ \dot{C}(t) = \phi I(t) - \xi_2 C(t) \\ \dot{A}(t) = \rho I(t) - \xi_1 A(t) \\ \dot{E}(t) = \psi S(t) - \mu E(t) \end{cases} \tag{5}$$

Finding the unique endemic equilibrium of this model is an easy but tedious job. Just like in Martin's paper, let's state the value of this equilibrium without computing it :

$$S^* = \frac{\Lambda}{\frac{\mathcal{N}-\frac{\mu+\theta+\psi}{\mu+\theta}\mathcal{D}}{\xi_1\xi_2+\xi_1\phi+\xi_2\rho} + \mu\frac{\mu+\theta+\psi}{\mu+\theta}}, \qquad E^* = \frac{\psi\Lambda}{(\mu+\theta)\frac{\mathcal{N}-\frac{\mu+\theta+\psi}{\mu+\theta}\mathcal{D}}{\xi_1\xi_2+\xi_1\phi+\xi_2\rho} + \mu(\mu+\theta+\psi)}$$

$$I^* = \frac{(\mathcal{N}-\frac{\mu+\theta+\psi}{\mu+\theta}\mathcal{D})\Lambda\xi_1\xi_2}{\left[\frac{\mathcal{N}-\frac{\mu+\theta+\psi}{\mu+\theta}\mathcal{D}}{\xi_1\xi_2+\xi_1\phi+\xi_2\rho} + \mu\frac{\mu+\theta+\psi}{\mu+\theta}\right]\mathcal{D}}, \qquad C^* = \frac{(\mathcal{N}-\frac{\mu+\theta+\psi}{\mu+\theta}\mathcal{D})\Lambda\xi_1\Phi}{\left[\frac{\mathcal{N}-\frac{\mu+\theta+\psi}{\mu+\theta}\mathcal{D}}{\xi_1\xi_2+\xi_1\phi+\xi_2\rho} + \mu\frac{\mu+\theta+\psi}{\mu+\theta}\right]\mathcal{D}},$$

$$A^* = \frac{(\mathcal{N}-\frac{\mu+\theta+\psi}{\mu+\theta}\mathcal{D})\Lambda\xi_2\rho}{\left[\frac{\mathcal{N}-\frac{\mu+\theta+\psi}{\mu+\theta}\mathcal{D}}{\xi_1\xi_2+\xi_1\phi+\xi_2\rho} + \mu\frac{\mu+\theta+\psi}{\mu+\theta}\right]\mathcal{D}}$$

Setting $\theta = 0$:

$$S^* = \frac{\Lambda}{\frac{\mathcal{N}-\frac{\mu+\psi}{\mu}\mathcal{D}}{\xi_1\xi_2+\xi_1\phi+\xi_2\rho} + \mu+\psi}, \qquad E^* = \frac{\psi\Lambda}{\frac{\mu\mathcal{N}-(\mu+\psi)\mathcal{D}}{\xi_1\xi_2+\xi_1\phi+\xi_2\rho} + \mu(\mu+\psi)}$$

$$I^* = \frac{(\mathcal{N}-\frac{\mu+\psi}{\mu}\mathcal{D})\Lambda\xi_1\xi_2}{\left[\frac{\mathcal{N}-\frac{\mu+\psi}{\mu}\mathcal{D}}{\xi_1\xi_2+\xi_1\phi+\xi_2\rho} + \mu+\psi\right]\mathcal{D}}, \qquad C^* = \frac{(\mathcal{N}-\frac{\mu+\psi}{\mu}\mathcal{D})\Lambda\xi_1\Phi}{\left[\frac{\mathcal{N}-\frac{\mu+\psi}{\mu}\mathcal{D}}{\xi_1\xi_2+\xi_1\phi+\xi_2\rho} + \mu+\psi\right]\mathcal{D}},$$

$$A^* = \frac{(\mathcal{N}-\frac{\mu+\psi}{\mu}\mathcal{D})\Lambda\xi_2\rho}{\left[\frac{\mathcal{N}-\frac{\mu+\psi}{\mu}\mathcal{D}}{\xi_1\xi_2+\xi_1\phi+\xi_2\rho} + \mu+\psi\right]\mathcal{D}}$$

Theorem. *The endemic equilibrium is globally asymptotically stable for* $\mathcal{R}_0 > 1$

Proof : This proof can be found in Silva and Torres' article [4]

5.6 Numerical simulations

The code can be found in the annex. We used the explicit Euler method to solve our ODE. As initial values, we took the same ones as Martin, namely $S(0) = 323911$, $I(0) = 61$ $C(0) = A(0) = 0$ and $E(0) = 5$. We first use the following parameters :

Notation	Meaning	Value
$N(0)$	Initial population	323972 ind
Λ	Recruitment rate	$13045\text{ind.year}^{-1}$
μ	Natural death rate	$1/69.54\text{year}^{-1}$
β	HIV transmission rate	0.7year^{-1}
η_C	Modification parameter	0.04
η_A	Modification parameter	1.35
ϕ	HIV treatment rate for I individuals	1year^{-1}
ψ	rate of PrEP treatment rate for S individuals	0.01year^{-1}
ρ	Default treatment rate for I individuals	0.1year^{-1}
α	AIDS treatment rate	0.33year^{-1}
ω	Default treatment rate for C individuals	0.09year^{-1}
d	AIDS induced death rate	0.2year^{-1}

These parameters are now such that $\mathcal{R}_0 = 3.49$, so we expect the disease to set in until it reaches the endemic equilibrium. Let's see the output of our simulations where figures 15, 16, 17, 18 and 19 respectively show the evolutions of the susceptibles, the infected, the patients under ART treatment, the infected with AIDS, and the people undergiong a PrEP treatment, with respect to time :

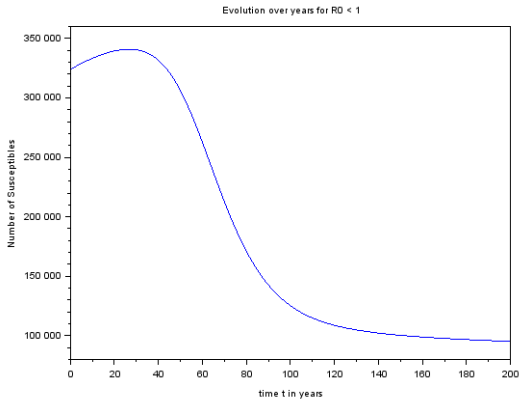

Figure 15: Evolution of S with respect to time when $\mathcal{R}_0 > 1$

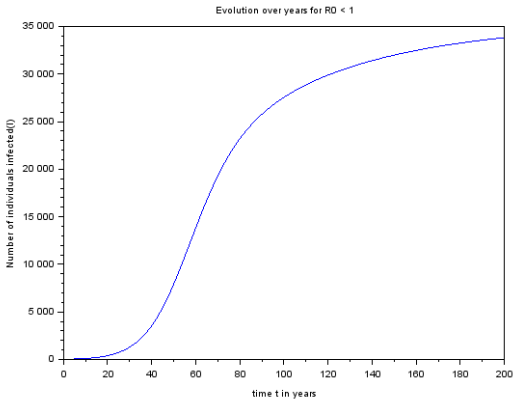

Figure 16: Evolution of I with respect to time when $\mathcal{R}_0 > 1$

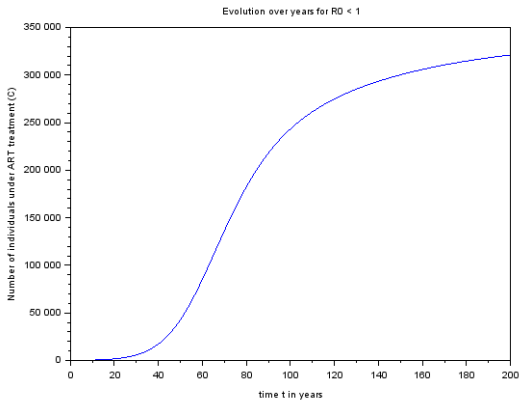

Figure 17: Evolution of C with respect to time when $\mathcal{R}_0 > 1$

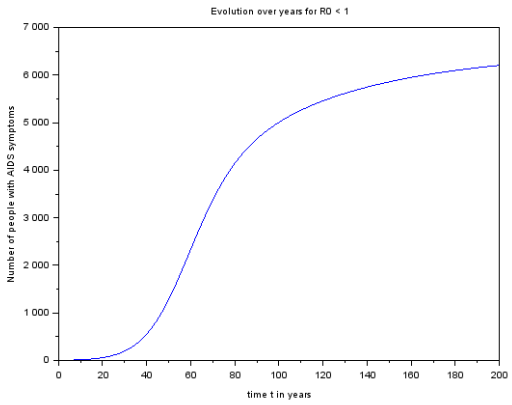

Figure 18: Evolution of A with respect to time when $\mathcal{R}_0 > 1$

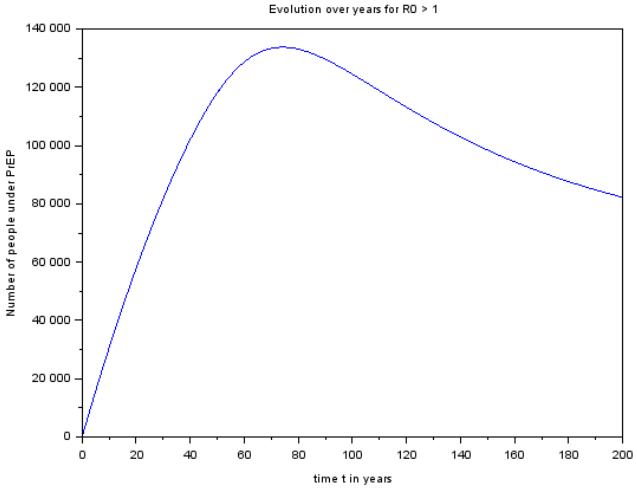

Figure 19: Evolution of E with respect to time when $\mathcal{R}_0 > 1$

Again, the numerical simulations confirm that whenever $\mathcal{R}_0 > 1$, which is in this case linked to a greater infectiousness rate β and a low rate of population starting PrEP, then the disease settles in the population until it reaches an equilibrium.

6 Simplified model for the spread of STIs with screening under PReP

We are now interested in looking at the spread of an STI, say syphilis, amongst the population following PrEP. For that purpose, we make a few relaxations. For instance, we consider that the total number of individuals in this model is constant, meaning that the global death rate μ is null, and that no individual joins the system over time. Moreover, we consider that people move from category S to category I in a constant fashion. Thus, only three categories of people are considered in this model :

- S, the susceptible individuals
- I, the infected ones
- Tr, the people undergoing treatment for syphilis

Here, we keep in mind that category I is unaware of being infected. We consider that this category gets screened every A units of time, $A \in \mathbb{R}$. In other words, by default, we consider that an individual that gets contaminated at time t will be aware of it and start treatment only when he gets screened, and thus he will be infectious during the interval. Figure 20 shows a visual representation of this model :

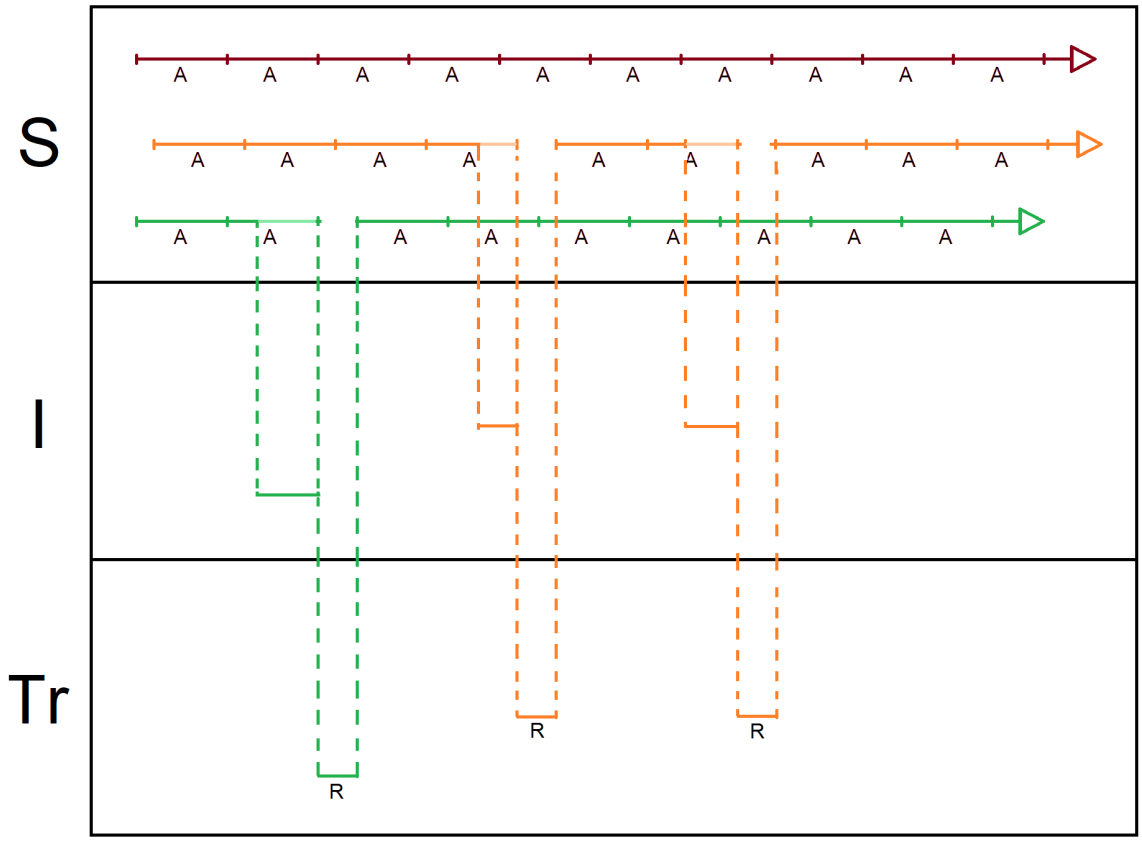

Figure 20: Evolution of three individuals with respect to time

and figure 21 shows the corresponding diagram of evolution : where R is the duration

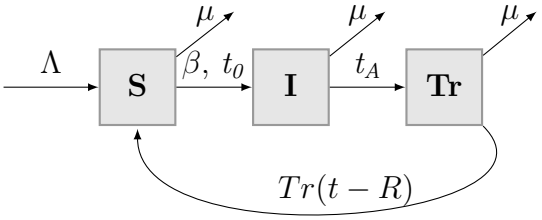

Figure 21: Evolution of the population

of sexual abstinence following the treatment. Let $x(t)$ be the amount of patients getting tested at time t and $\beta(t)$ be the infection rate at time t. Then $I(t) = \int_{t-A}^{t} x(s)\beta(s)ds$. We are now facing a delay differential equation. Solving such an ODE analytically is beyond our current mathematical knowledge. Moreover, this requires us to know the value of some parameters relating to syphilis, i.e. the infectious rate of this disease amongst the population under PrEP. In order to estimate this parameter, we would need to know how many tests came out positive each day in a follow-up of a population under PrEP. What follows is an idea of how to estimate the number of infected persons at a given moment. We set ourselves again in the case where the total population of the people undergoing a PrEP treatment is not constant and we denote this category of people at each instant of time t by $E(t)$. Here, $E(t) = S(t) + I(t) + Tr(t)$ .We recall that these patients get screenings for other STIs aswell as for HIV every 3 months (92 days in average). Let A_j be the average number of patients that get tested on day j. We assume that this number can be estimated in the following way :

$$A_j = \frac{\sum_{i=j-1}^{j-92} E(i)}{92^2}$$

Let B_j be the number of patients amongst A_j whose test comes out positive, meaning that they are aware of their infection on day j. We consider that sexual intercourses are uniformaly distributed over time, thus we can uniformaly distribute the B_j individuals whose test came out positive over the last 92 days as an estimate of when they got infected. Thus, the estimate number of people that have been infected on day d is :

$$i(d) = \sum_{i=1}^{92} \frac{B_{d+92-i}}{92}$$

$i(d)$ is the number of new infections on day d. However, we want $I(d)$, which is the total number of infected people on day d. Then we can estimate it as follows :

$$I(d) = \sum_{t=0}^{A} i(t)$$

Once we have this estimate, we are able to model the future number of people infected at each day, and thus we would be able to construct the algorithm describing figure 20 and 21.

7 Difficulties encountered and what the research taught us

Despite our efforts , we have not been able to collect a relevant set of data that would have allowed us to estimate the needed parameters for a sample of the French population.
Moreover, we have been facing the difficulties linked to the creation of an exploitable model, namely the non-negativeness of our variables as we study populations, to ensure well-posedness of our model.
This research made us discover new mathematical notions and taught us to confront ourselves to unknown tools and how to tackle them.

8 Conclusion

In the context of this research project, we presented a couple of models as well as their analytical and numerical studies. We have studied the two main models of Silva and Torres [4] which was further developped in Thomas Martin's research paper [3]. The study has shown the importance of being able to control the parameters linked with the spread of HIV. For instance, higher use of condoms makes β, the HIV transmission rate, decrease and thus $\mathcal{R}_0$ decrease. Moreover, screening campaigns would encourage people to get screenings more frequently and allow ϕ, the HIV treatment rate for infected individuals, to increase and α, the AIDS treatment rate, to also increase, resulting in a decrease of $\mathcal{R}_0$. All of this is the power of both individuals and public policies, so the future of HIV could lie in our hands.

It would be interesting to study the impact of the time lapse between to screenings in the case people under PrEP. For instance, what would be the nature of the relationship between the number of infected people and this time lapse?

References

[1] Michael W. Traeger, Vincent J. Cornelisse, Jason Asselin, Brian Price, Norman J. Roth, Jeff Willcox, Ban Kiem Tee, Christopher K. Fairley, Christina C. Chang, Jude Armishaw, Olga Vujovic, Matthew Penn, Pauline Cundill, George Forgan-Smith, John Gall, Claire Pickett, Luxi Lal, Anne Mak, Tim D. Spelman, Long Nguyen, Dean A. Murphy, Kathleen E. Ryan, Carol El-Hayek, Michael West, Simon Ruth, Colin Batrouney, John T. Lockwood, Jennifer F. Hoy, Margaret E. Hellard, Mark A. Stoové, Edwina J. Wright, and for the PrEPX Study Team. Association of HIV Preexposure Prophylaxis With Incidence of Sexually Transmitted Infections Among Individuals at High Risk of HIV InfectionAssociation of HIV Preexposure Prophylaxis With Incidence of STIsAssociation of HIV Preexposure Prophylaxis With Incidence of STIs. *JAMA*, 321(14):1380–1390, 04 2019.

[2] JamesWatmough P.van den Driessche. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical Biosciences*, 180(1-2):29–48, 2002.

[3] Thomas Martin. Mathematical modeling and study of the impact of prep on stis development. *Master Mathematiques en Action UCBL*, 2018.

[4] Cristiana J. Silva and Delfim F. M. Torres. Modeling and optimal control of hiv/aids prevention through prep. 2017.

9 Annex

SICA model with $\mathcal{R}_0 > 1$

```
Lambda=13045;
na=1.3;
nc=0.04;
mu=1/69;
beta=0.752;
rho=0.1;
phi=1;
alpha=0.33;
omega=0.09;
d=1;
ep1=alpha+mu+d;
ep2=omega+mu;
ep3=rho+phi+mu;

function [Sd,Id,Cd,Ad]=SICAdev(S,I,C,A)
    N=S+I+C+A;
    Sd=Lambda-(1/N)*beta*(I+nc*C+na*A)*S-mu*S;
    Id=(1/N)*beta*(I+nc*C+na*A)*S-(rho+phi+mu)*I+alpha*A+omega*C;
    Cd=(phi*I-(omega+mu)*C);
    Ad=rho*I-(alpha+mu+d)*A;
endfunction

h=0.001

numbr=200000

SICA=zeros(4,numbr)
SICA(1,1)=323911
SICA(2,1)=61
SICA(3,1)=0
SICA(4,1)=0
N=SICA(1,1)+SICA(2,1)+SICA(3,1)+SICA(4,1);

for k=1:(numbr-1)
    [Sd,Id,Cd,Ad]=SICAdev(SICA(1,k),SICA(2,k),SICA(3,k),SICA(4,k))
    SICA(1,k+1)=SICA(1,k)+h*Sd
    SICA(2,k+1)=SICA(2,k)+h*Id
    SICA(3,k+1)=SICA(3,k)+h*Cd
    SICA(4,k+1)=SICA(4,k)+h*Ad
end


R0=(beta*(ep2*(ep1+rho*na)+nc*phi*ep1))/(mu*(ep2*(rho+ep1)+phi*ep1+rho*d)
```

```
+rho*omega*d);
denomR0=(mu*(ep2*(rho+ep1)+phi*ep1+rho*d)+rho*omega*d)

lambda_eq=denomR0*(R0-1)/(ep1*ep2+phi*ep1+rho*ep2)

S_eq=Lambda/(lambda_eq+mu)
I_eq=lambda_eq*Lambda*ep1*ep2/((lambda_eq+mu)*denomR0)
C_eq=phi*Lambda*lambda_eq*ep1/((lambda_eq+mu)*denomR0)
A_eq=rho*Lambda*lambda_eq*ep2/((lambda_eq+mu)*denomR0)

clf();
figure(1);
figure(1).background=8;
plot((1:numbr)*0.001,[SICA(1,:) linspace(S_eq,S_eq,numbr)])
hl=legend([Susceptibles;Equilibrium␣S*]);
xlabel("time t in years")
ylabel(Number␣of␣Susceptibles)
title("Evolution over years for R0 > 1 " )
figure(2);
figure(2).background=8;
plot((1:numbr)*0.001,[SICA(2,:) linspace(I_eq, I_eq,numbr) ] )
hl=legend([Infected; Equilibrium␣I*);
xlabel("time t in years")
ylabel(Number␣of␣individuals␣infected(I))
title("Evolution over years for R0 > 1 " )
figure(3);
figure(3).background=8;
plot((1:numbr)*0.001,[SICA(3,:) linspace(C_eq, C_eq,numbr)] )
hl=legend([under␣ART␣treatment␣C;Equilibrium␣C*]);
xlabel("time t in years")
ylabel(Number␣of␣individuals␣under␣ART␣treatment␣(C))
title("Evolution over years for R0 > 1 " )
figure(4);
figure(4).background=8;
plot((1:numbr)*0.001,[SICA(4,:) linspace(A_eq, A_eq, numbr)])
hl=legend([A(t) ; Equilibrium␣A*]);
xlabel("time t in years")
ylabel(Number␣of␣people␣with␣AIDS␣symptoms)
title("Evolution over years for R0 > 1 " )
```

SICAE model with $\mathcal{R}_0 < 1$

```
Lambda=9045;
na=1.3;
nc=0.04;
mu=1/69;
beta=0.1;
rho=0.1;
phi=1;
psi=0.01;
theta=0;
alpha=0.33;
omega=0.09;
d=0.2;
ep1=alpha+mu+d;
ep2=omega+mu;
ep3=rho+phi+mu;

function [Sd,Id,Cd,Ad,Ed]=SICAEdev(S,I,C,A,E)
    N=S+I+C+A+E;
    Sd=Lambda-(1/N)*beta*(I+nc*C+na*A)*S-(mu+psi)*S+theta*E;
    Id=(1/N)*beta*(I+nc*C+na*A)*S-(rho+phi+mu)*I+alpha*A+omega*C;
    Cd=(phi*I-(omega+mu)*C);
    Ad=rho*I-(alpha+mu+d)*A;
    Ed=psi*S-(theta+mu)*E
endfunction

h=0.001

numbr=50000

SICAE=zeros(5,numbr)
SICAE(1,1)=323911
SICAE(2,1)=61
SICAE(3,1)=0
SICAE(4,1)=0
SICAE(5,1)=5
N=SICAE(1,1)+SICAE(2,1)+SICAE(3,1)+SICAE(4,1)+SICAE(5,1);

for k=1:(numbr-1)
    [Sd,Id,Cd,Ad,Ed]=SICAEdev(SICAE(1,k),SICAE(2,k)
    ,SICAE(3,k),SICAE(4,k),SICAE(5,k))
    SICAE(1,k+1)=SICAE(1,k)+h*Sd
    SICAE(2,k+1)=SICAE(2,k)+h*Id
    SICAE(3,k+1)=SICAE(3,k)+h*Cd
    SICAE(4,k+1)=SICAE(4,k)+h*Ad
```

```
    SICAE(5,k+1)=SICAE(5,k)+h*Ed
end


R0=(beta*(ep2*(ep1+rho*na)+nc*phi*ep1))/(mu*(ep2*(rho+ep1)+phi*ep1
+rho*d)+rho*omega*d);
denomR0=(mu*(ep2*(rho+ep1)+phi*ep1+rho*d)+rho*omega*d)
numR0=(beta*(ep2*(ep1+rho*na)+nc*phi*ep1))

R0E=(theta + mu)*numR0/((theta+psi+mu)*denomR0)
deg1=(numR0-denomR0*(mu + theta + psi)/(mu+theta))/(ep1*ep2+ep1*phi+ep2*rho)
deg2=(deg1+mu*(mu+theta+psi)/(mu+theta))

lambda_eq=denomR0*(R0-1)/(ep1*ep2+phi*ep1+rho*ep2)

S_eq=Lambda/deg2
E_eq=psi*Lambda/((mu+theta)*deg1+mu*(mu+psi+theta))
I_eq=(numR0-denomR0*(mu + theta + psi)/(mu+theta))*Lambda*ep1*ep2/(deg2*denomR0)
C_eq=(numR0-denomR0*(mu + theta + psi)/(mu+theta))*Lambda*ep1*phi/(deg2*denomR0)
A_eq=(numR0-denomR0*(mu + theta + psi)/(mu+theta))*Lambda*rho*ep2/(deg2*denomR0)

clf();
figure(1);
figure(1).background=8;
plot((1:numbr)*0.001, SICAE(1,:))
//hl=legend([Susceptibles;Equilibrium␣S*]);
xlabel("time t in years")
ylabel(Number␣of␣Susceptibles)
title("Evolution over years for R0 < 1 " )
figure(2);
figure(2).background=8;
plot((1:numbr)*0.001,SICAE(2,:))
//hl=legend([Infected; Equilibrium␣I*]);
xlabel("time t in years")
ylabel(Number␣of␣individuals␣infected(I))
title("Evolution over years for R0 < 1 " )
figure(3);
figure(3).background=8;
plot((1:numbr)*0.001,SICAE(3,:))
//hl=legend([under␣ART␣treatment␣C;Equilibrium␣C*]);
xlabel("time t in years")
ylabel(Number␣of␣individuals␣under␣ART␣treatment␣(C))
title("Evolution over years for R0 < 1 " )
figure(4);
figure(4).background=8;
plot((1:numbr)*0.001,SICAE(4,:))
//hl=legend([A(t); Equilibrium␣A*]);
xlabel("time t in years")
```

```
ylabel(Number␣of␣people␣with␣AIDS␣symptoms)
title("Evolution over years for R0 < 1 " )
figure(5);
figure(5).background=8;
plot((1:numbr)*0.001,SICAE(5,:))
//hl=legend([A(t); Equilibrium␣A*]);
xlabel("time t in years")
ylabel(Number␣of␣people␣under␣PrEP)
title("Evolution over years for R0 < 1 " )
```

SICAE model with $\mathcal{R}_0 > 1$

```
Lambda=9045;
na=1.3;
nc=0.04;
mu=1/69;
beta=0.7;
rho=0.1;
phi=1;
psi=0.01;
theta=0;
alpha=0.33;
omega=0.09;
d=0.2;
ep1=alpha+mu+d;
ep2=omega+mu;
ep3=rho+phi+mu;

function [Sd,Id,Cd,Ad,Ed]=SICAEdev(S,I,C,A,E)
    N=S+I+C+A+E;
    Sd=Lambda-(1/N)*beta*(I+nc*C+na*A)*S-(mu+psi)*S+theta*E;
    Id=(1/N)*beta*(I+nc*C+na*A)*S-(rho+phi+mu)*I+alpha*A+omega*C;
    Cd=(phi*I-(omega+mu)*C);
    Ad=rho*I-(alpha+mu+d)*A;
    Ed=psi*S-(theta+mu)*E
endfunction

h=0.001

numbr=200000

SICAE=zeros(5,numbr)
SICAE(1,1)=323911
SICAE(2,1)=61
SICAE(3,1)=0
SICAE(4,1)=0
SICAE(5,1)=5
N=SICAE(1,1)+SICAE(2,1)+SICAE(3,1)+SICAE(4,1)+SICAE(5,1);
```

```
for k=1:(numbr-1)
    [Sd,Id,Cd,Ad,Ed]=SICAEdev(SICAE(1,k),SICAE(2,k),SICAE(3,k),SICAE(4,k),SICAE(5,k))
    SICAE(1,k+1)=SICAE(1,k)+h*Sd
    SICAE(2,k+1)=SICAE(2,k)+h*Id
    SICAE(3,k+1)=SICAE(3,k)+h*Cd
    SICAE(4,k+1)=SICAE(4,k)+h*Ad
    SICAE(5,k+1)=SICAE(5,k)+h*Ed
end


R0=(beta*(ep2*(ep1+rho*na)+nc*phi*ep1))/(mu*(ep2*(rho+ep1)+phi*ep1+rho*d)+rho*omega*d
denomR0=(mu*(ep2*(rho+ep1)+phi*ep1+rho*d)+rho*omega*d)
numR0=(beta*(ep2*(ep1+rho*na)+nc*phi*ep1))

R0E=(theta + mu)*numR0/((theta+psi+mu)*denomR0)
deg1=(numR0-denomR0*(mu + theta + psi)/(mu+theta))/(ep1*ep2+ep1*phi+ep2*rho)
deg2=(deg1+mu*(mu+theta+psi)/(mu+theta))

lambda_eq=denomR0*(R0-1)/(ep1*ep2+phi*ep1+rho*ep2)

S_eq=Lambda/deg2
E_eq=psi*Lambda/((mu+theta)*deg1+mu*(mu+psi+theta))
I_eq=(numR0-denomR0*(mu + theta + psi)/(mu+theta))*Lambda*ep1*ep2/(deg2*denomR0)
C_eq=(numR0-denomR0*(mu + theta + psi)/(mu+theta))*Lambda*ep1*phi/(deg2*denomR0)
A_eq=(numR0-denomR0*(mu + theta + psi)/(mu+theta))*Lambda*rho*ep2/(deg2*denomR0)

clf();
figure(1);
figure(1).background=8;
plot((1:numbr)*0.001, SICAE(1,:))
//hl=legend([Susceptibles;Equilibrium␣S*]);
xlabel("time t in years")
ylabel(Number␣of␣Susceptibles)
title("Evolution over years for R0 > 1 " )
figure(2);
figure(2).background=8;
plot((1:numbr)*0.001,SICAE(2,:))
//hl=legend([Infected; Equilibrium␣I*]);
xlabel("time t in years")
ylabel(Number␣of␣individuals␣infected(I))
title("Evolution over years for R0 > 1 " )
figure(3);
figure(3).background=8;
plot((1:numbr)*0.001,SICAE(3,:))
//hl=legend([under␣ART␣treatment␣C;Equilibrium␣C*]);
xlabel("time t in years")
ylabel(Number␣of␣individuals␣under␣ART␣treatment␣(C))
```

```
title("Evolution over years for R0 > 1 " )
figure(4);
figure(4).background=8;
plot((1:numbr)*0.001,SICAE(4,:))
//hl=legend([A(t); Equilibrium␣A*]);
xlabel("time t in years")
ylabel(Number␣of␣people␣with␣AIDS␣symptoms)
title("Evolution over years for R0 > 1 " )
figure(5);
figure(5).background=8;
plot((1:numbr)*0.001,SICAE(5,:))
//hl=legend([A(t); Equilibrium␣A*]);
xlabel("time t in years")
ylabel(Number␣of␣people␣under␣PrEP)
title("Evolution over years for R0 > 1 " )
```