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A simple model of HIV epidemic in Italy: the role of
the anti-retroviral treatment

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Abstract

In the present paper we propose a simple ODE model to describe the evolution of HIV epidemic in Italy. The model considers a single population of susceptibles, without distinction of high-risk groups within the general population, and accounts for the presence of immigration, modelling its effects on both the general demography and the dynamics of the infected subpopulations. To represent the intra-host disease progression, the untreated infected population is distributed over four compartments in cascade according to the CD4 counts. A further compartment is added to represent infected people under antiretroviral therapy. The values of the model parameters not reported in the literature are assessed by fitting available epidemiological data over the decade $2003 \div 2013$. Predictions until year 2025 are computed, showing the benefits of the earlier eligibility of patients to the initiation of antiretroviral therapy. Analytical results about properties of the model in its time-invariant form are provided, in particular the global stability of the equilibrium points is established either in the absence and in the presence of infected among immigrants.

Key words: HIV epidemic, HAART, immigration, epidemic ODE models, stability of equilibrium points

AMS subject classifications: 92D30, 92B05, 93D05

1. Introduction

The treatment of Human Immunodeficiency Virus-1 (HIV) infection presently faces extraordinary opportunities and challenges in achieving durable efficacy in previously untreated subjects. In fact, even though it does not allow a complete elimination of the virus from several tissue and blood cell reservoirs, antiretroviral treatment has been shown to decrease viral replication as detected by HIV ribonucleic acid (RNA) in plasma [21, 27]. The virological control obtained on treatment, documented by undetectable levels of HIV RNA in plasma, has been shown to improve the immunological setting of patients, increasing the number of CD4+ cells, the subset of lymphocytes mainly affected by the virus [18].

Since high rates of HIV RNA control have been shown on treatment both in recent cohort studies and in clinical trials [28], this achievement has been associated with a marked decrease in several opportunistic infections and clinical comorbidities [31, 10]. Besides, a successful virological control has also beneficial effects in reducing the spread of HIV infection through sexual contacts, as documented by studies evaluating antiretroviral treatment as a tool for the prevention of HIV transmission to healthy partners [12].

The decrease in CD4 cell counts during HIV infection in the absence of therapy has been used in the past to obtain a marker of immune depletion in order to advise in favor or against the introduction of antiretroviral therapy. Since AIDS-related opportunistic infections generally appear when CD4 are lower than 200 cells/μL, previous guidelines suggested the initiation of antiretroviral treatment when CD4 decreased below 350 cells/μL [32]. On the contrary, recent clinical evidences suggest that the early introduction of antiretroviral therapy at diagnosis, regardless of CD4 cell counts, may have benefits on clinical outcomes [29]. Indeed, it is expected that this change in antiretroviral prescription, known as 'test and treat' strategy, will also reduce the spread of HIV infection to the uninfected population [33].

According to estimates by the Italian National Institute of Health, about 120,000 individuals are living with HIV in Italy [7]. A recent investigation indicates that about 90,000 are in care at clinical Centers and 77,000 are receiving ARVs [6]. The proportion of patients in therapeutic failure is presently unknown, even if clinical trial data show high prevalence of HIV undetectability on treatment (80-90%). The future trends of HIV spread in the Italian population will be determined by the burden of subjects with detectable HIV RNA, thus depending on several factors, such as the appropriate use of treatment options and the effort to anticipate the initiation of antiretroviral therapy. An appropriate prediction of the future trends in HIV epidemics will likely help to enlighten the possible impact of different public health and clinical strategies on the spread of the infection.

Since the seminal paper by May and Anderson [20], a large number of studies have been devoted to mathematical models of HIV epidemic. We mention some recent investigations [14, 13, 15] that establish global dynamics properties of classes of models of interest for the HIV epidemic. Other mathematical models have been developed either to assess the impact of larger treatment availability on the spread of HIV [17, 9], showing a beneficial impact on the reduction of the infection incidence rate, and to assess the effects of virus mutation and of drug resitance onset [2, 26, 19].

Many papers aim at describing the epidemic evolution in single countries or in single geografic regions (see e.g [25, 22, 34]). Concerning Italy, Arcà *et al.* built a detailed multi-stage ODE model for the HIV transmission in Latium, with eight groups differentiated by sex and routes of infection [1]. With focus on the epidemic among drug users in Latium, Iannelli *et al.* [16] proposed an age-structured model validated against data on the number of new AIDS cases.

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Camoni *et al.* [7], by considering different high-risk subpopulations, and gathering a number of different statistical informations, gave an estimate of the history of the epidemic in Italy, taking also into account the practice of therapy. Nevertheless, no predictions are available about the possible impact of an early antiretroviral treatment and 'test and treat' strategies on HIV epidemic in specific European Countries, such as Italy.

In order to forecast the possible impact of new strategies in antiretroviral management, a differential equation model is developed in the present paper to describe the evolution of HIV epidemic in Italy for the years $2003 \div 2025$. Unlike the above mentioned studies, we try to describe the HIV epidemic in Italy by considering a single population of susceptibles, thus making no reference to high-risk groups. The main motivation of our choice is that of keeping the model simple, also in view of future developments about the effects of virus resistance to antiretroviral drugs. The model presented here takes into account the extent of immigration and its effect, on both the general demography and the dynamics of the infected subpopulations.

In Section 2, the ODE model is formulated, and in Section 3 the parameter values are assessed, in part by means of best fitting of available data over the decade $2003 \div 2013$. Predictions until year 2025 are reported in Section 4, showing the benefits of early initiation of the antiretroviral therapy. Section 5 reports some results of the analysis of the model in its time-invariant version, in particular the global stability of the equilibrium points is established either in the absence and in the presence of HIV infection among immigrants. Some concluding remarks (Section 6) complete the work.

2. Model formulation

The present model describes the dynamics of HIV infection in Italy by assuming that the heterosexual/homosexual activity and the exchange of needles among drug users are the only significant modalities of HIV transmission. Therefore, the mother-child transmission and the transmission by blood transfusion are disregarded. This choice is supported by recent reports of the Italian National Institute of Health [4, 5], indicating that the percentages of new diagnoses in 2012 and 2013 related to transmission routes not involving inter-individual contacts are less than 2%.

The HIV epidemic in Italy is still mainly concentrated in high risk sub-populations (injected drug users, male homosexuals, female sex workers, multi-partners heterosexual male). However, there are evidences of some spreading of the infection outside these groups. Indeed, 32% of infected people in 2013 was estimated to belong to the remaining general population [7].

On the basis of this evidence and for the sake of simplicity, we assume in our model that the population susceptible of infection, $S(t)$, consists of all the uninfected Italians having age in the range $20 \div 70$ years. We choose these age limits for susceptibles since the 97.6% of the new diagnoses recorded in 2012 and 2013 falls in that age range [4, 5]. Concerning the Italian demography, we will take into account the presence of immigration, since immigration in the last years is comparable with the birth rate of the resident population [24]. As a consequence, the role of immigration in the dynamics of HIV infected population cannot be disregarded *a priori*.

To represent the intra-host disease progression, the untreated infected population is distributed over four compartments in cascade according to the CD4 counts. In particular, according to [1, 26], we distinguish the infected population $I(t)$ into the following sub-populations:

- $I_1(t)$: number of individuals in the primary infection stage;

- $I_2(t)$: infected individuals with CD4 count > 350 cells/μL;

- $I_3(t)$: infected individuals with CD4 count in the range 200÷350 cells/μL;

- $I_4(t)$: infected individuals with CD4 count < 200 cells/μL.

Compartment I_4 represents individuals in the AIDS stage. A further compartment, $I_5(t)$, is added to account for infected people under HAART (highly active anti-retroviral therapy), introduced in Italy since 1996. Compartment I_5 includes both patients achieving complete and partial viral suppression [26].
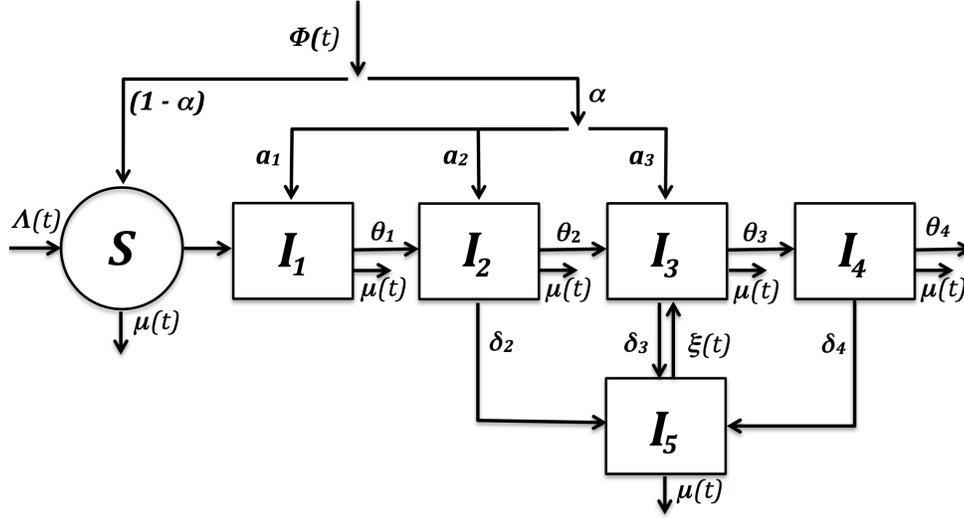

Figure 1: Block diagram of the model.

Under the above assumptions, we can describe the dynamics of susceptible and infected sub-populations by the following ODE system (see the block diagram of Figure 1):

$$\dot{S}(t) = \Lambda(t) + (1-\alpha)\Phi(t) - \mu(t)S(t) - \left(\sum_{n=1}^{5}\beta_n I_n(t)\right)S(t)$$

$$\dot{I}_1(t) = a_1\alpha\Phi(t) + \left(\sum_{n=1}^{5}\beta_n I_n(t)\right)S(t) - (\theta_1+\mu(t))I_1(t),$$

$$\dot{I}_2(t) = a_2\alpha\Phi(t) + \theta_1 I_1(t) - (\theta_2+\mu(t)+\delta_2)I_2(t),$$

$$\dot{I}_3(t) = a_3\alpha\Phi(t) + \theta_2 I_2(t) - (\theta_3+\mu(t)+\delta_3)I_3(t) + \xi(t)I_5(t),$$

$$\dot{I}_4(t) = \theta_3 I_3(t) - (\theta_4+\mu(t)+\delta_4)I_4(t),$$

$$\dot{I}_5(t) = \delta_2 I_2(t) + \delta_3 I_3(t) + \delta_4 I_4(t) - (\xi(t)+\mu(t))I_5(t),$$

(1)

where $\Lambda(t)$ is the net input rate in the susceptible population due to the balance between the inflow and the outflow through the selected age boundaries; $\Phi(t)$ is the rate of adult immigration; α is the HIV prevalence among immigrants; a_1, a_2, a_3 are the fractions subdividing the flow $\alpha\Phi(t)$ into the compartments I_1, I_2, I_3 respectively ($a_1 + a_2 + a_3 = 1$); $\mu(t)$ is the pro capite loss rate owing to causes not related to the infection (namely, natural death plus emigration); β_n, $n = 1,\ldots,5$, is the infectivity of individuals in compartment I_n; θ_n, $n = 1,2,3$ is the pro capite disease progression rate from compartment I_n to compartment I_{n+1}; θ_4 is the pro capite death rate from AIDS. Note that, since immigration of people in AIDS stage and the presence

of immigrants under HAART appear rather unlikely, no input from immigration is assumed into compartments I_4 and I_5. Moreover, we assume

$$a_n = \frac{1/\theta_n}{1/\theta_1 + 1/\theta_2 + 1/\theta_3}, \quad n = 1, 2, 3, \tag{2}$$

that is the fractions a_n are taken proportional to the average transit time of the corresponding stage.

The possibility of starting the treatment from different stages of the disease is taken into account by the pro capite treatment rates, δ_n, of infected individuals in compartment I_n, $n = 2, 3, 4$. The possibility that treatment is initiated from the primary infection stage is instead disregarded, since at present it is difficult to have a diagnosis of HIV positivity at this stage. $\xi(t)$ is the pro capite exit rate from compartment I_5, and it represents voluntary interruptions or failures of treatment. Although it may be questioned whether the disease in patients exiting from therapy actually evolves as in naive infected individuals, we adopted this simpler view. Therefore we assumed that people exiting from I_5 return, for simplicity, into *one* of the stages of the active disease progression. We identify this stage as the stage I_3, in view of some clinical observations on the time interval typically elapsed from interruption of successful therapy and the falling of CD4 counts below the level of 200 cells/μL (2 years in average, [23]).

We assumed in model (1) a bilinear form of the incidence rate, instead of the more usual standard incidence in which the infective population is normalized to the total population size. This choice brings about some advantages for the model analysis, as we will see later. On the other hand, in our case, the dynamics under bilinear incidence and under standard incidence are expected to be very similar. In fact, the Italian population in the age range $20 \div 70$ years was almost constant from January 1st 2003 to January 1st 2013, changing of only 2% from 38.378 to 39.139 millions of individuals [24].

3. Parameter tuning and data fitting

The behaviour of the model has been tested by comparison with epidemiological data over the years $2003 \div 2013$. Precisely, we considered the following data:

- number of infected individuals over the years $2003 \div 2013$, plus the number of treated individuals at the end of 2012, estimated by the UNAIDS tool EPP/Spectrum [7];

- number of treated individuals at the end of 2012 from data of clinical Centres [6];

- number of new AIDS cases over the years $2003 \div 2013$ [5];

- number of deaths from AIDS over the years $2003 \div 2012$ [5].

Data reported by the National Institute of Statistics [24] were used to estimate the time-course of the demographic quantities Λ, Φ, and μ. The rate of immigration in Italy (per day) is shown in Figure 2 as a piecewise constant function. Although, the age profile of immigrants as a function of time is actually unknown, a survey conducted in 2001 suggests that a percentage of about 70% of immigrants was in the age range $20 \div 70$ years [3]. Thus, we adopted such a percentage to calculate $\Phi(t)$ from the immigration rate of Figure 2. Since no data about the prevalence of HIV infection among immigrants were available, we kept for α the prevalence value estimated in the Italian population [7]. The pro capite loss rate $\mu(t)$, taken as a piecewise constant function

where the generic constant μ_k represents the mean loss rate over the year k. The vale μ_k was estimated according to

$$\mu_k = \frac{M_k}{\bar{N}_k \cdot 365},$$

where M_k is the number of deaths (not caused by AIDS) plus the number of emigrants during the year k, in the age range of interest, and $\bar{N}_k$ is the average number of inhabitants of the selected ages during year k. The function $\mu(t)$ is plotted in Figure 3. It can be noted that $\mu(t)$ changes only slightly with time, thus we assumed $\mu(t)$ constant and equal to its average value $\bar{\mu} = 1.1 \cdot 10^{-5}$ day^{-1}.
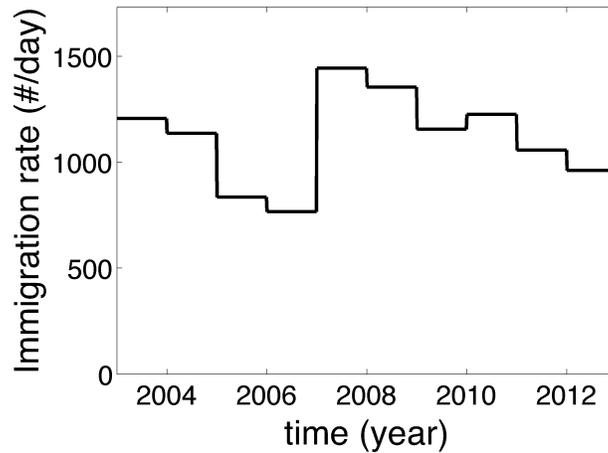

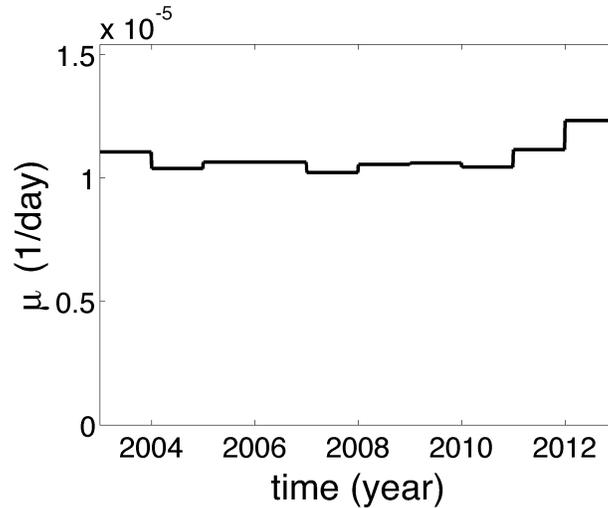Figure 2: Rate of immigration in Italy averaged over each year.

Figure 3: Pro capite loss rate averaged over each year.

Let $N_{[20,70]}(t)$ be the number of Italians, both non-infected and infected, in the $20 \div 70$ age range. We can write the following approximate balance equation

$$\frac{dN_{[20,70]}(t)}{dt} = \Lambda(t) + \Phi(t) - \mu(t)N_{[20,70]}(t). \tag{3}$$

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that does not include the loss due to the ageing of infected people beyond age 70 – which can be neglected with respect to the same loss of non-infected individuals taken into account by Λ – and the deaths from AIDS, totally negligible compared to the non-AIDS deaths.

Eq. (3) allows the estimation of $\Lambda(t)$. For simplicity, we estimated the average value, $\bar{\Lambda}$, of $\Lambda(t)$ over the decade, by a least square fitting of the solution of Equation 3, with $\mu(t) = \bar{\mu}$ and the calculated $\Phi(t)$, to the data on $N_{[20,70]}$. The estimated $\bar{\Lambda}$ is equal to -156.36 individuals per day and the obtained best fitting of $N_{[20,70]}$ data is reported in Figure 4. The negative value of $\bar{\Lambda}$ reflects the current scarce natality in Italy and the progressive increase of the mean population age.
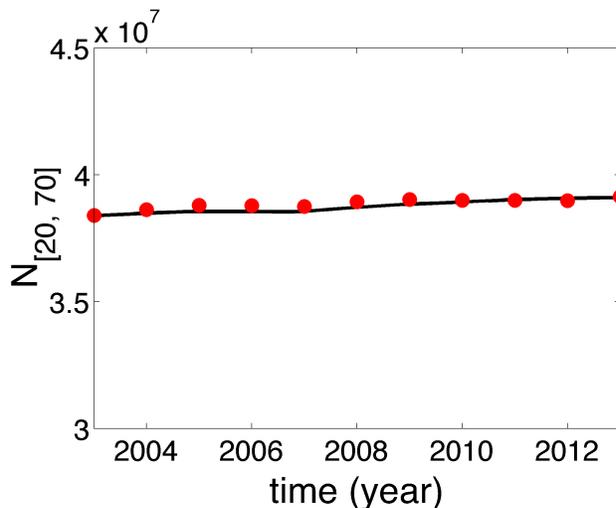

Figure 4: Evolution of the Italian population in the $20 \div 70$ years age range: data (number of inhabitants at the beginning of the indicated year), circle; prediction by Equation (3), solid line.

Concerning the disease progression, the parameters θ_n, $n = 1, \ldots, 4$, have been chosen according to [35, 26] and are reported in Table 1. Note that $\sum_{n=1}^{4} \theta_n^{-1} \simeq 11$ years, which is the typical duration of the disease for untreated individuals [35]. It is well known that the infectivity depends on the stage of the disease, with the largest infectivity occurring at the primary stage. We fixed the ratios β_n/β_2, $n = 1, 3, 4$ following [26]. The infectivity of treated subjects was instead supposed to be very low (see Table 1), despite the presence of patients with only a partial viral suppression, assuming that all the individuals under therapy conform to a safe behaviour. The exit rate from the treatment $\xi(t)$ has been assumed variable in the interval $2003 \div 2013$, with $1/\xi(t)$ ranging linearly from 15 to 30 years. The assumption of a decreasing $\xi(t)$ is in agreement with the observed reduction of resistance in Italy in the reference decade, [11]. The parameters characterizing $1/\xi(t)$, that is the mean residence time in the compartment I_5, were calibrated using clinical information and a preliminary trial and error fitting of the number of new AIDS cases and of deaths from AIDS.

The remaining parameters β_2, δ_2, δ_3, δ_4 were estimated from all the available data by means of a weighted least squares procedure, using weights equal to the inverse of the squared data. In order to reduce the effect of the transient response on the fitting curves, the ODE system was integrated starting from year 1996 with an initial condition for I_5 equal to zero, according to the introduction of HAART in that year. The number of deaths from AIDS in each year was fitted by the integral of $\theta_4 I_4(t)$ over the year of interest, whereas the number of new AIDS cases

by the integral of $\delta_4 I_4(t)$. The quantity $\delta_4 I_4(t)$ can be intended as the notification rate of new AIDS cases since the usual practice consists in treating a patient as soon as AIDS is diagnosed. Figures 5-6 show the fitting curves and Table 1 reports all the values of the parameters.
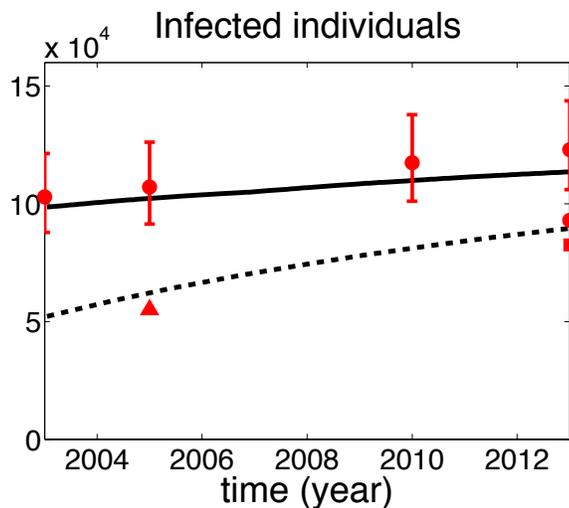

Figure 5: Time-course of the number of HIV infected individuals and of HAART treated patients in Italy, over the years $2003 \div 2013$. Median values estimated by Camoni et al. [7], circles (bars represent the difference between the 3rd and the 1st quartiles); measurement of the number of treated patients at the end of 2012 [6], square. Model predictions: infected, black solid line; treated patients, black dashed line. Estimate of patients under treatment at year 2005, triangle (communicated by C. Balotta).
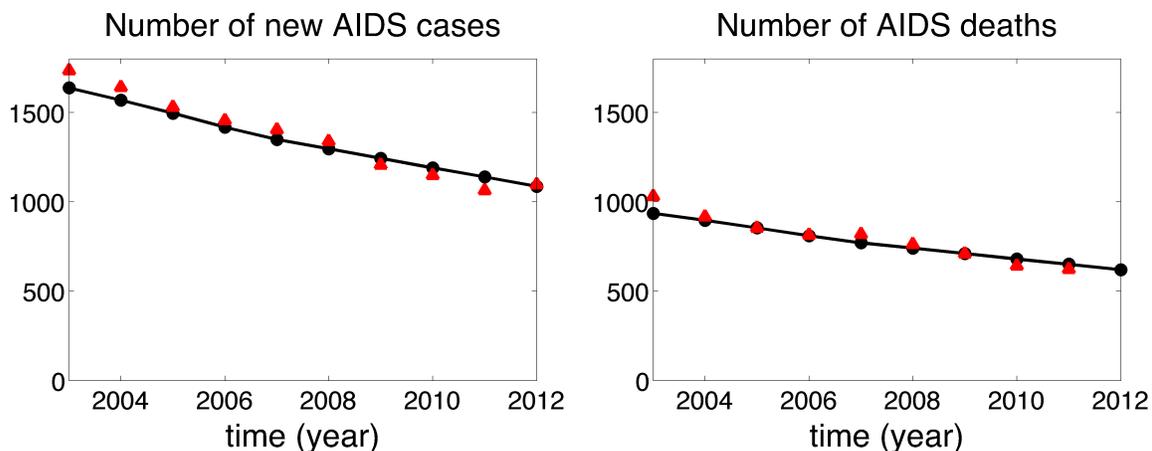

Figure 6: New cases of AIDS and number of deaths by AIDS in Italy. Data from [5], red triangles; model predictions, black circles.

Table 1: Parameter values.

Parameters	Value	Source
$\bar{\Lambda}$	-156.36 #/day	[24]
$\Phi(t = 2013)$	672.70 #/day	[24]
$\bar{\mu}$	$1.1 \cdot 10^{-5}$ day^{-1}	[24]
α	$3.2 \cdot 10^{-3}$	[7]
$1/\xi(t = 2003)$	$5,475$ days	Assumed
$1/\xi(t = 2013)$	$10,950$ days	Assumed
θ_1	$2.86 \cdot 10^{-2}$ day^{-1}	[26]
θ_2	$4.57 \cdot 10^{-4}$ day^{-1}	[26]
θ_3	$7.83 \cdot 10^{-4}$ day^{-1}	[26, 35]
θ_4	$1.8 \cdot 10^{-3}$ day^{-1}	[26, 35]
β_2	$3.55 \cdot 10^{-12}$	Estimated
β_1/β_2	4.5	[26]
β_3/β_2	1.125	[26]
β_4/β_2	1.667	[26]
β_5/β_2	0.01	Assumed
δ_2	$5.96 \cdot 10^{-19}$ day^{-1}	Estimated
δ_3	$2.3 \cdot 10^{-3}$ day^{-1}	Estimated
δ_4	$3.2 \cdot 10^{-3}$ day^{-1}	Estimated

4. Predictions for the years 2013-2025

We start by predicting the HIV epidemic evolution assuming that $\Lambda(t)$, $\mu(t)$, $\Phi(t)$ and $\xi(t)$ are constant and equal to the corresponding values at 2013. All the remaining parameters are set to the values reported in Table 1. The best fitting of the available data, as reported in the previous section, suggests that, in the $2003 \div 2013$ period, the pro capite treatment rate of AIDS patients was the largest, followed by the treatment rate of patients with CD4 count between 350 and 200 cells/μl. Early treatment with higher CD4 counts resulted negligible ($\delta_2 \approx 10^{-19}$ day^{-1}). The epidemic evolution was firstly predicted until year 2025, keeping the same treatment eligibility profile (reference evolution). Next, to investigate the effect of changing the eligibility criterion, we hypothesize two scenarios: a) δ_3 is increased to the estimated value of δ_4 reported in Table 1; b) both δ_2 and δ_3 are increased to the value of δ_4. For both scenarios, we can observe that anticipating the initiation of treatment results in a lower number either of new AIDS cases and AIDS deaths (see Figure 7). Concerning the evolution of infected people, only scenario b) shows a remarkable effect (see Figure 8). In particular, it leads to a rapid increase in the number of treated individuals, whereas the number of total infected lowers slowly. In scenario b), the model predicts for the year 2025 a 43% reduction either in the new cases of AIDS and in the number of AIDS deaths, compared to the values of the reference evolution, and a 5% reduction in the total number of infected individuals. From the inspection of the incidence rate time-course (not
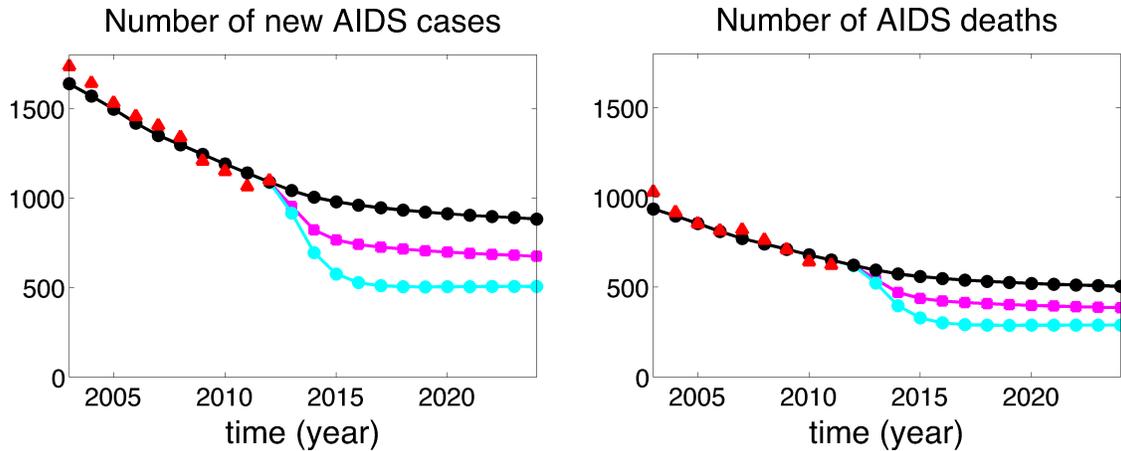
Figure 7: Predictions of new cases of AIDS and number of AIDS deaths. Parameters δ_2, δ_3, δ_4 as in Table 1 (reference prediction), black circles; δ_2, δ_4 unchanged and $\delta_3 = \delta_4$, magenta squares; δ_4 unchanged and $\delta_2 = \delta_3 = \delta_4$, cyan circles.

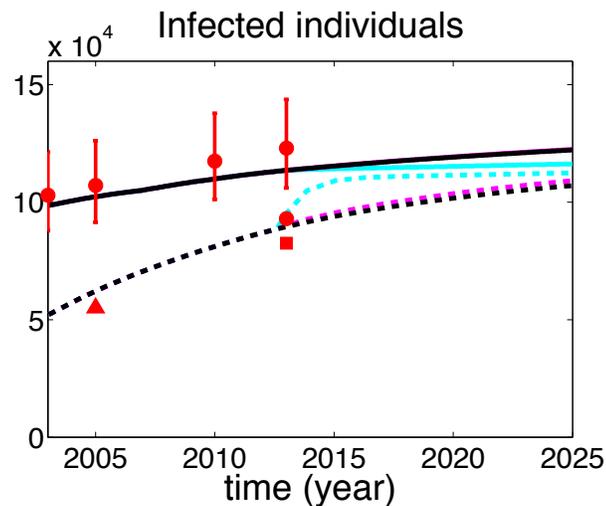shown), we could notice a 69% decrease of newly infected subjects at year 2025.

Figure 8: Predictions of the number of infected individuals: total infected, solid lines; infected under therapy, dashed lines. Reference prediction, black. Prediction with $\delta_3 = \delta_4$, magenta. Prediction with $\delta_2 = \delta_3 = \delta_4$, cyan. Note that solid lines are substantially overlapping.

Finally, we investigated the effect of changing the treatment exit rate. In particular, we first assumed $1/\xi(t)$ linearly increasing in 2013-2025 with the same slope of the previous decade. This case, in which $\xi(t)$ is decreasing, represents a continuative improvement of the treatment efficiency. Next, we assumed $1/\xi(t)$ decreasing in 2013-2025, still linearly but with opposite slope of the previous decade. This simulation, with increasing $\xi(t)$, is intended to mimic a relapse of resistance in the prediction period. The results are reported in Figures 9, 10. No apparent effect can be noticed on the evolution of the infected individuals, whereas, as expected, the number of treated individuals decreases when $\xi(t)$ is supposed to increase. By contrast, either

for decreasing and for increasing $\xi(t)$, the number of new cases of AIDS and the number of AIDS deaths are remarkably affected (see Figure 10). In particular, for both these quantities, the decreasing trend established over $2003 \div 2013$ is dramatically reverted if $\xi(t)$ is supposed to increase.
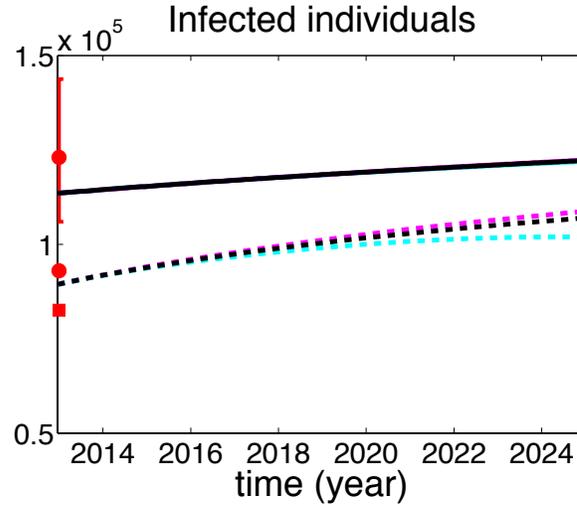

Figure 9: Predictions of the number of infected individuals: total infected, solid lines; infected under therapy, dashed lines. Reference prediction, black. $1/\xi(t)$ linearly increasing, magenta. $1/\xi(t)$ linearly decreasing, cyan. Note that solid lines are substantially overlapping.
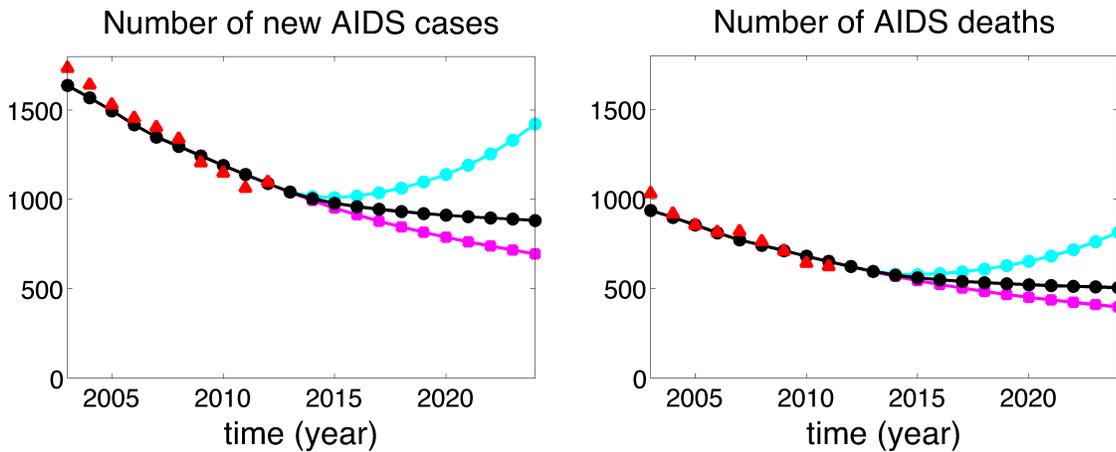
Figure 10: Predictions of new cases of AIDS and number of AIDS deaths. $\delta_2, \delta_3, \delta_4$ as in Table 1 (reference prediction), black circles; $1/\xi(t)$ linearly increasing, magenta squares; $1/\xi(t)$ linearly decreasing, cyan circles.

5. Analysis of asymptotic properties

In this section, we establish the stability properties of the time-invariant version of the model described by Eqs. (1), where the functions $\Lambda(t)$, $\mu(t)$, $\Phi(t)$, $\xi(t)$ are assumed constant. Namely,

we will study the ODE system:

$$\dot{S}(t) = \Lambda + (1-\alpha)\Phi - \mu S(t) - \left(\sum_{n=1}^{5} \beta_n I_n(t)\right) S(t)$$

$$\dot{I}_1(t) = a_1\alpha\Phi + \left(\sum_{n=1}^{5} \beta_n I_n(t)\right) S(t) - (\theta_1 + \mu) I_1(t),$$

$$\dot{I}_2(t) = a_2\alpha\Phi + \theta_1 I_1(t) - (\theta_2 + \mu + \delta_2) I_2(t),$$

$$\dot{I}_3(t) = a_3\alpha\Phi + \theta_2 I_2(t) - (\theta_3 + \mu + \delta_3) I_3(t) + \xi I_5(t), \tag{4}$$

$$\dot{I}_4(t) = \theta_3 I_3(t) - (\theta_4 + \mu + \delta_4) I_4(t),$$

$$\dot{I}_5(t) = \delta_2 I_2(t) + \delta_3 I_3(t) + \delta_4 I_4(t) - (\xi + \mu) I_5(t),$$

with $0 \le \alpha \le 1$ and with the assumption

$$\Lambda + (1-\alpha)\Phi > 0. \tag{5}$$

The above assumption prevents the susceptible population from the extinction. Indeed, if $S = 0$ (5) implies $\dot{S} > 0$. Note that (5) is satisfied with $\Lambda = \bar{\Lambda}$, $\Phi = \Phi(t = 2013)$ (see Table 1).

We observe that the set

$$\Omega = \left\{ (S, I_1, \ldots, I_5) \in I\!\!R_+^6 \mid S + \sum_{n=1}^{5} I_n \le \frac{\Lambda + \Phi}{\mu} \right\}, \tag{6}$$

where $I\!\!R_+^6$ denotes the non-negative orthant of $I\!\!R^6$, is invariant for the system (4). This property can be easily established by examining the directions of the vector field defined by (4) on the boundary of $I\!\!R_+^6$ and taking into account that

$$\dot{N}(t) = \dot{S}(t) + \sum_{n=1}^{5} \dot{I}_n(t) \quad = \quad \Lambda + \Phi - \mu N(t) - \theta_4 I_4(t)$$

$$\le \quad \Lambda + \Phi - \mu N(t), \tag{7}$$

for non-negative $I_4(t)$. The above inequality, in fact, implies

$$N(t) \le N(t_0)e^{-\mu(t-t_0)} + \frac{\Lambda + \Phi}{\mu} \left(1 - e^{-\mu(t-t_0)}\right), \tag{8}$$

which in turn implies $N(t)$ bounded by $(\Lambda + \Phi)/\mu$ for any initial state in Ω.

Also, we remark that if an equilibrium point of system (4) exists in $I\!\!R_+^6$, it necessarily belongs to Ω. Let E be such an equilibrium, and N^*, I_4^* be the corresponding values of the total population and of the number of individuals in the AIDS stage respectively. Since E is an equilibrium, we have

$$\Lambda + \Phi - \mu N^* - \theta_4 I_4^* = 0, \tag{9}$$

whereas if E were such that $N^* > (\Lambda + \Phi)/\mu$ we would get the contradiction:

$$\Lambda + \Phi - \mu N^* - \theta_4 I_4^* < 0.$$

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5.1. Existence and stability of equilibria for $\alpha = 0$

Denoting by $E = (S^*, I_1^*, \ldots, I_5^*)$ a generic equilibrium point of system (4) with $\alpha = 0$, i.e. without infected among immigrants, we have that E must satisfy the following algebraic system

$$\Lambda + \Phi = \mu S^* + \left(\sum_{n=1}^{5} \beta_n I_n^* \right) S^*,$$

$$Q_1 I_1^* = \left(\sum_{n=1}^{5} \beta_n I_n^* \right) S^*,$$

$$Q_2 I_2^* = \theta_1 I_1^*,$$

$$Q_3 I_3^* = \theta_2 I_2^* + \xi I_5^*,$$

$$Q_4 I_4^* = \theta_3 I_3^*,$$

$$Q_5 I_5^* = \delta_2 I_2^* + \delta_3 I_3^* + \delta_4 I_4^*,$$

$$(10)$$

where

$$\begin{aligned}
Q_1 &= \theta_1 + \mu, \\
Q_2 &= \theta_2 + \mu + \delta_2, \\
Q_3 &= \theta_3 + \mu + \delta_3, \\
Q_4 &= \theta_4 + \mu + \delta_4, \\
Q_5 &= \xi + \mu.
\end{aligned} \tag{11}$$

From the last four equations in (10) we obtain:

$$I_n^* = m_n I_1^*, \quad n = 2, \ldots, 5, \tag{12}$$

where

$$m_2 = \frac{\theta_1}{Q_2},$$

$$m_3 = \frac{\theta_2 + \delta_2(\xi/Q_5)}{Q_3 - \delta_3(\xi/Q_5) - \theta_3(\delta_4/Q_4)(\xi/Q_5)} m_2,$$

$$m_4 = \frac{\theta_3}{Q_4} m_3,$$

$$m_5 = \frac{\delta_2}{Q_5} m_2 + \frac{\delta_3}{Q_5} m_3 + \frac{\delta_4}{Q_5} m_4.$$

$$(13)$$

Introducing the notation

$$\eta = \beta_1 + \beta_2 m_2 + \beta_3 m_3 + \beta_4 m_4 + \beta_5 m_5,$$

and taking into account (12), the first two equations of the system (10) can be rewritten as

$$\Lambda + \Phi - \mu S^* - \eta I_1^* S^* = 0,$$
$$I_1^* (\eta S^* - Q_1) = 0. \tag{14}$$

System (14) admits two different solutions

$$S^* = \frac{\Lambda + \Phi}{\mu}, \ I_1^* = 0 \qquad \text{or} \qquad S^* = \frac{Q_1}{\eta}, \ I_1^* = \left(\frac{\Lambda + \Phi}{Q_1} - \frac{\mu}{\eta} \right), \tag{15}$$

meaning that system (4) has in Ω the disease-free equilibrium E_{df}

$$S^* = \frac{\Lambda + \Phi}{\mu}, \qquad I_n^* = 0, \ n = 1, \ldots, 5, \tag{16}$$

and, if and only if $(\Lambda + \Phi)\eta > \mu Q_1$, the positive endemic equilibrium E_{en}

$$S^* = \frac{Q_1}{\eta}, \qquad I_n^* = m_n \left(\frac{\Lambda + \Phi}{Q_1} - \frac{\mu}{\eta} \right), \quad n = 1, \ldots, 5, \tag{17}$$

where $m_1 = 1$.

The stability analysis of the disease-free equilibrium has been performed by means of the reproduction number R, computed exploiting the method proposed in [30], after verifying that our dynamical model satisfies all the structural hypothesis required. Then, let us define the vectors

$$f = \begin{bmatrix} \left(\displaystyle\sum_{n=1}^{5} \beta_n I_n(t) \right) S(t) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \tag{18}$$

$$v = \begin{bmatrix} Q_1 I_1(t) \\ -\theta_1 I_1(t) + Q_2 I_2(t) \\ -\theta_2 I_2(t) - \xi I_5(t) + Q_3 I_3(t) \\ -\theta_3 I_3(t) + Q_4 I_4(t) \\ -\delta_2 I_2(t) - \delta_3 I_3(t) - \delta_4 I_4(t) + Q_5 I_5(t) \end{bmatrix} \tag{19}$$

where the generic entry f_i represents the rate of appearance of new infections in compartment i while the entry v_i represents the sum of the transfer rates of individuals exiting from (positive sign) and entering (negative sign) compartment i. Let us also compute the Jacobian matrices of vectors f, v at the equilibrium E_{df}

$$F = \nabla f|_{E_{df}} = \frac{\Lambda + \Phi}{\mu} \begin{bmatrix} \beta_1 & \beta_2 & \beta_3 & \beta_4 & \beta_5 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix} \tag{20}$$

$$V = \nabla v|_{E_{df}} = \begin{bmatrix} Q_1 & 0 & 0 & 0 & 0 \\ -\theta_1 & Q_2 & 0 & 0 & 0 \\ 0 & -\theta_2 & Q_3 & 0 & -\xi \\ 0 & 0 & -\theta_3 & Q_4 & 0 \\ 0 & -\delta_2 & -\delta_3 & -\delta_4 & Q_5 \end{bmatrix}. \tag{21}$$

According to [8], the reproduction number is defined as the spectral radius of the next generation matrix FV^{-1}. So, taking into account the expression of the inverse matrix of V,

$$V^{-1} = \frac{1}{Q_1} \begin{bmatrix} 1 & * & * & * & * \\ m_2 & * & * & * & * \\ m_3 & * & * & * & * \\ m_4 & * & * & * & * \\ m_5 & * & * & * & * \end{bmatrix}, \tag{22}$$

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where only the first column of V^{-1} is needed for the computation of R, and recalling the expression of F given by (20), we obtain

$$R = \rho \left(FV^{-1} \right) = \frac{\Lambda + \Phi}{\mu} \frac{\eta}{Q_1}, \tag{23}$$

where $\rho(\cdot)$ is the spectral radius operator. Note that condition (5) guarantees $R > 0$.

It is useful to rewrite the expression of the endemic equilibrium in terms of R, given by (23), as

$$S^* = \frac{\Lambda + \Phi}{\mu} \frac{1}{R}, \qquad I_n^* = m_n \frac{Q_1}{\mu(R-1)}, \quad n = 1, \ldots, 5, \tag{24}$$

showing that the endemic equilibrium exists if and only if $R > 1$.

Thanks to the bilinear form of the incidence rate, it can be verified that model (4) with $\alpha = 0$ belongs to the class of models studied by Guo et al. in [15]. Then, their stability analysis of the disease-free equilibrium and of the possible endemic equilibrium applies to our model. We have the following results.

Theorem 5.1. *When $\alpha = 0$ and $\Lambda + \Phi > 0$, R is positive and the disease-free equilibrium E_{df} exists for any value of R. For $R \leq 1$, E_{df} is globally asymptotically stable in Ω, while for $R > 1$ is unstable.*

Proof. See the proof of Theorem 4.1 in [15]. It can be easily verified that our model satisfies all the basic assumptions (H_1)-(H_8), as well as the additional hypotheses (A_1), (A_2) assumed by the Authors to prove the global stability of the disease-free equilibrium for $R \leq 1$ and its instability for $R > 1$ (see Appendix). ∎

Theorem 5.2. *When $\alpha = 0$ and $\Lambda + \Phi > 0$, the endemic equilibrium E_{en} exists if and only if $R > 1$, and it is globally asymptotically stable in $\Omega \setminus \{E_{df}\}$.*

Proof. The proof of the existence comes directly from Eq. (24). Indeed, vector (24) is positive if and only if $R > 1$. For the global stability of the endemic equilibrium, see the proof of Theorem 5.1 in [15]. The additional hypothesis assumed in [15] hold in our case (see Appendix).

In view of the analysis of model (4) with $\alpha > 0$, however, we report here how the proof of the general result in [15] can be specialized in our case. The global stability of E_{en} can be indeed proved considering the following Lyapunov function

$$L(S, I_1, \ldots, I_5) = c_1 \left(S - S^* - S^* \ln \left(\frac{S}{S^*} \right) \right) + \sum_{n=1}^{5} c_n \left(I_n - I_n^* - I_n^* \ln \left(\frac{I_n}{I_n^*} \right) \right), \tag{25}$$

which, for positive coefficients c_n, has the following properties:

$$\begin{aligned} L(S, I_1, \ldots, I_5) = 0 &\Leftrightarrow (S, I_1, \ldots, I_5) = (S^*, I_1^*, \ldots, I_5^*), \\ L(S, I_1, \ldots, I_5) > 0, &\quad \forall (S, I_1, \ldots, I_5) \neq (S^*, \ldots, I_5^*). \end{aligned} \tag{26}$$

From Eq. (25) it follows

$$\dot{L}(S, I_1, \ldots, I_5) = c_1 \left(1 - \frac{S^*}{S} \right) \dot{S} + \sum_{n=1}^{5} c_n \left(1 - \frac{I_n^*}{I_n} \right) \dot{I}_n. \tag{27}$$

By exploiting either the equations of the dynamic system (4) and the equilibrium equations in (10), and introducing also the compact notation $s = S/S^*$, $i_n = I_n/I_n^*$, $n = 1, \ldots, 5$, we obtain

$$
\begin{aligned}
\dot{L}(S, I_1, \ldots, I_5) = & \\
c_1 & \left(\mu S^* \left(2 - s - \frac{1}{s} \right) + \sum_{n=1}^{5} \beta_n S^* I_n^* \left(2 - \frac{s\, i_n}{i_1} - \frac{1}{s} - i_1 + i_n \right) \right) + c_2 \left(\theta_1 I_1^* \left(1 - \frac{i_1}{i_2} - i_2 + i_1 \right) \right) + \\
c_3 & \left(\theta_2 I_2^* \left(1 - \frac{i_2}{i_3} - i_3 + i_2 \right) + \xi I_5^* \left(1 - \frac{i_5}{i_3} - i_3 + i_5 \right) \right) + c_4 \left(\theta_3 I_3^* \left(1 - \frac{i_3}{i_4} - i_4 + i_3 \right) \right) + \\
c_5 & \left(\delta_2 I_2^* \left(1 - \frac{i_2}{i_5} - i_5 + i_2 \right) + \delta_3 I_3^* \left(1 - \frac{i_3}{i_5} - i_5 + i_3 \right) + \delta_4 I_4^* \left(1 - \frac{i_4}{i_5} - i_5 + i_4 \right) \right).
\end{aligned}
$$

(28)

Such a function is non-positive in the interior of Ω by choosing the Lyapunov coefficients $c_1, \ldots, c_5$ according to the method proposed in [15] (see the Appendix for details), namely

$$
\begin{aligned}
c_1 &= \Theta_1 \Theta_3 \left(\Theta_2 \sum_{n=2}^{4} \Delta_n + \Xi_5 \Delta_2 \right), \\
c_2 &= \sum_{n=2}^{5} B_n \Theta_3 \left(\Theta_2 \sum_{n=2}^{4} \Delta_n + \Xi_5 \Delta_2 \right), \\
c_3 &= \Theta_1 \Theta_3 \left(B_3 \sum_{n=2}^{4} \Delta_n + B_4 \sum_{n=2}^{4} \Delta_n + B_5 \sum_{n=3}^{4} \Delta_n \right), \\
c_4 &= \Theta_1 \left(B_3 \Xi_5 \Delta_4 + B_4 \left(\Theta_2 \sum_{n=2}^{4} \Delta_n + \Xi_5 \left(\Delta_2 + \Delta_4 \right) \right) + B_5 \Delta_4 (\Theta_2 + \Xi_5) \right), \\
c_5 &= \Theta_1 \Theta_3 \left(\Xi_5 \sum_{n=3}^{5} B_n + \Theta_2 B_5 \right),
\end{aligned}
$$

(29)

where

$$
\begin{aligned}
\Theta_1 &= \theta_1 I_1^*, & \Theta_2 &= \theta_2 I_2^*, & \Theta_3 &= \theta_3 I_3^*, \\
\Delta_2 &= \delta_2 I_2^*, & \Delta_3 &= \delta_3 I_3^*, & \Delta_4 &= \delta_4 I_4^*, \\
\Xi_5 &= \xi I_5^*, & B_n &= \beta_n S^* I_n^*, \; n = 2, \ldots, 5.
\end{aligned}
$$

(30)

Therefore, we obtain $\dot{L}(S, I_1, \ldots, I_5) \leq 0$, with $\dot{L}(S, I_1, \ldots, I_5) = 0$ only in $\{E_{en}\}$ (see Appendix). This proves the asymptotic stability of E_{en} in the interior of Ω. Since on the boundary of Ω out of the disease-free equilibrium the vector field of our system points inwards, the basin of attraction of E_{en} can be extended to $\Omega \setminus \{E_{df}\}$. ∎

In order to illustrate the role of antiviral treatment, it may be of interest to compute the reproduction number R for different treatment scenarios. With $\Lambda = \bar{\Lambda}$, $\Phi = \Phi(t = 2013)$, $\alpha = 0$, and setting the values of the other parameters as in Table 1, R is equal to 0.836. In the absence of treatment ($\delta_n = 0$, $n = 2, 3, 4$), R decreases to 0.759. So we notice that, in general, treatment is not necessarily accompanied by a lower value of R, since treatment implies a longer average life-time of infected individuals, and then may imply a greater pro capite number of infections. However, it is also possible that treatment decreases R: making δ_2 and δ_3 equal to δ_4, R decreases to 0.465; with $\xi = 0$ and keeping the other parameter values of Table 1 (i.e. in case of life-long successful therapy), $R = 0.590$.

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5.2. Existence and stability of positive equilibria for $\alpha > 0$

In this section we report the equilibrium analysis of model (4) when $\alpha > 0$, i.e. in the presence of infected among immigrants.

For the generic equilibrium point, the following algebraic system holds

$$
\Lambda + (1 - \alpha)\Phi = \mu S^* + \left(\sum_{n=1}^{5} \beta_n I_n^* \right) S^*,
$$

$$
Q_1 I_1^* = \left(\sum_{n=1}^{5} \beta_n I_n^* \right) S^* + a_1 \alpha \Phi,
$$

$$
Q_2 I_2^* = a_2 \alpha \Phi + \theta_1 I_1^*,
$$

$$
Q_3 I_3^* = a_3 \alpha \Phi + \theta_2 I_2^* + \xi I_5^*,
$$

$$
Q_4 I_4^* = \theta_3 I_3^*,
$$

$$
Q_5 I_5^* = \delta_2 I_2^* + \delta_3 I_3^* + \delta_4 I_4^*,
$$

(31)

where the quantities Q_n, $n = 1, \ldots, 5$, are given by (11). From the last four equations in (31) we obtain:

$$
I_n^* = q_n + m_n I_1^*, \quad n = 2, \ldots, 5,
$$

(32)

where the coefficients m_n are explicitly given in (13), while the terms q_n are defined as follows:

$$
q_2 = \frac{a_2 \alpha \Phi}{Q_2},
$$

$$
q_3 = \frac{a_3 \alpha \Phi}{Q_3 - \delta_3(\xi/Q_5) - \theta_3(\delta_4/Q_4)(\xi/Q_5)} + \frac{\theta_2 + \delta_2(\xi/Q_5)}{Q_3 - \delta_3(\xi/Q_5) - \theta_3(\delta_4/Q_4)(\xi/Q_5)} q_2,
$$

$$
q_4 = \frac{\theta_3}{Q_4} q_3,
$$

$$
q_5 = \frac{\delta_2}{Q_5} q_2 + \frac{\delta_3}{Q_5} q_3 + \frac{\delta_4}{Q_5} q_4.
$$

(33)

Theorem 5.3. *When $\alpha > 0$ and $\Lambda + (1 - \alpha)\Phi > 0$, a unique positive equilibrium exists in Ω and it is globally asymptotically stable.*

Proof. Recalling the definition of η given in Section 5.1 and introducing the notation

$$
\gamma = \beta_2 q_2 + \beta_3 q_3 + \beta_4 q_4 + \beta_5 q_5,
$$

from the first two equations of (31) and from equations (32) we obtain

$$
S^* = \frac{\Lambda + (1 - \alpha)\Phi}{\gamma + \eta I_1^* + \mu},
$$

(34)

and the quadratic equation in the variable I_1^*

$$
a I_1^{*2} + b I_1^* + c = 0,
$$

where

$$
a = -Q_1 \eta, \quad b = (\Lambda + (1 + a_1 \alpha - \alpha)\Phi)\eta - Q_1(\gamma + \mu),
$$

$$
c = a_1 \alpha \Phi \mu + (\Lambda + (1 + a_1 \alpha - \alpha)\Phi)\gamma.
$$

From (5) we have $c > 0$, and then, since $a < 0$, there exists a unique positive solution for I_1^*, that is

$$I_1^* = \zeta + \sqrt{\zeta^2 + \nu},$$

$$\zeta = \frac{(\Lambda + (1 + a_1\alpha - \alpha)\Phi)\eta - Q_1(\gamma + \mu)}{2Q_1\eta}, \quad \nu = \frac{a_1\alpha\Phi\mu + (\Lambda + (1 + a_1\alpha - \alpha)\Phi)\gamma}{Q_1\eta}. \tag{35}$$

Note that if a positive equilibrium exists, Eq. (34) implies that (5) must hold. Thus, (5) is a necessary and sufficient condition for the existence of the unique positive equilibrium defined by Eqs. (34), (35), and (32).

The stability of such an endemic equilibrium can be proved considering the same Lyapunov function defined by (25). Indeed, from the derivative of L given by (27), from system (4) with $\alpha > 0$, and from the equilibrium equations (31), we obtain

$$\dot{L}(S, I_1, \ldots, I_5) = \dot{L}'(S, I_1, \ldots, I_5) + \dot{L}''(S, I_1, \ldots, I_5), \tag{36}$$

where

$$\dot{L}'(S, I_1, \ldots, I_5) = \sum_{n=1}^{3} c_n a_n \alpha \Phi \left(2 - i_n - \frac{1}{i_n}\right), \tag{37}$$

while the term $\dot{L}''(S, I_1, \ldots, I_5)$ equals the r.h.s. of (28). Since in the proof of Theorem 5.2 it has been demonstrated the non-positivity of the function (28), we have $\dot{L}''(S, I_1, \ldots, I_5) \leq 0$ for the same choice of the coefficients c_n given in (29), (30). Conversely, it is easy to see that for any (positive) choice of c_n, it results $\dot{L}'(S, I_1, \ldots, I_5) \leq 0$ since it is $(2 - i_n - 1/i_n) \leq 0$ for the arithmetic-mean/geometric-mean inequality. Moreover, it is $\dot{L}(S, I_1, \ldots, I_5) = 0$ only in the set $\{(S^*, I_1^*, \ldots, I_5^*)\}$. Such a property can be easily verified by simultaneously equating to zero all the polynomials in the brackets of Eq. (37), as well as of Eqs. (43), (45). ∎

Note that if the weaker condition $\Lambda + (1 - \alpha)\Phi \geq 0$ were required instead of (5), when $\Lambda + (1 - \alpha)\Phi = 0$ a unique equilibrium would still exist with $S^* = 0$ and $I_1^*, \ldots, I_5^* > 0$, namely with the whole population infected.

6. Concluding remarks

The present paper presents a mathematical model developed to assess the impact of early treatment strategies in Italy. If the treatment is initiated regardless of CD4 cell counts at diagnosis, a significant impact over AIDS incidence and mortality is predicted, provided that the trend of reduced resistance to drug, observed in the decade $2003 \div 2013$, is maintained in time. Moreover, the model forecasts a relevant decrease in the number of newly infected individuals, thus suggesting benefits from the implementation of a 'test and treat' strategy for the control of HIV infection, in agreement with other theoretical studies (see e.g [17]).

The formal analysis of the model has allowed to establish the existence of equilibria and their global stability, classifying them on the basis of the prevalence of infected among immigrants. Only in the case in which the fraction of infected among immigrants is zero, the disease-free equilibrium exists and a threshold parameter for its stability can be identified in the reproduction number. The value of the reproduction number, moreover, has a non-trivial relationship with the parameters characterizing the dynamics of the compartment related to patients under treatment.

However, the knowledge of equilibria and their stability is scarcely useful for predicting the HIV epidemic over reasonable time horizons. Numerical simulations have shown indeed a very

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slow convergence to the equilibrium point (> 100 years), since the time from infection to death is quite long, even in untreated subjects ($\sum_{n=1}^{4} \theta_n^{-1} \simeq 11$ years, with the values of Table 1).

It may be questioned whether the disease progression in patients for whom therapy is interrupted or is no longer effective can be equated with the progression experienced by naive infected individuals. Thus, it would be worthy to design and study a little more complex model in which different disease progressions for naive and previously treated patients are considered. Finally, it cannot be guaranteed that the trend of reduced drug resistance will continue over the next decade. Therefore, a model of the evolution in Italy of the resistance to different classes of drugs is still needed and it is the main goal of our future work.

Acknowledgments

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Appendix

It can be easily verified that the basic hypotheses (H_1)-(H_8) assumed in [15] are satisfied by model (4) with $\alpha = 0$.

Additional properties are required to prove the global asymptotic stability of the disease-free equilibrium and the global asymptotic stability of the unique endemic equilibrium. In this section, it is shown that all these additional properties are satisfied by our model.

With this aim we introduce the following notation:

24.

- $\chi(S) = \Lambda + \Phi - \mu S$, growth rate of model (4) with $\alpha = 0$;

- $g_n(S, I_n) = \beta_n S I_n$, $n = 1, \ldots, 5$, bilinear incidence term for infections occurring by contact of susceptibles with infected in stage n;

- $\psi_n(I_n) = Q_n I_n$, $n = 1, \ldots, 5$, removal rate from compartments I_n, including natural death, disease progression, possibly treatment initiation/interruption or death due to the disease (see the equations of Q_n in (11));

- $\omega_{j,n}(I_n) = \sigma_{j,n} I_n$, $1 \le j, n \le 5$, transfer rate from compartment I_n to compartment I_j, where $\sigma_{2,1} = \theta_1$, $\sigma_{3,2} = \theta_2$, $\sigma_{4,3} = \theta_3$, $\sigma_{3,5} = \xi$ and $\sigma_{5,n} = \delta_n$, $n = 2, 3, 4$, while $\sigma_{j,n} = 0$ for all the remaining pairs of indexes.

We also denote by $\tilde{S}$ the number of susceptible individuals at the disease-free equilibrium (that is the value of S at which the growth rate vanishes, i.e. $\chi(\tilde{S}) = 0$) and with S^*, I_n^*, $n = 1, \ldots, 5$, the values of the state variables at the endemic equilibrium. We also define the function $\varphi(S) = S$. On the basis of the above notation, we rewrite hypotheses (A_1), (A_2) and (B_1)-(B_4) required in [15] showing that they are satisfied by our rate functions and by the chosen $\varphi(S)$:

(A1): For $n = 1, \ldots, 5$, we have

$$g_n(S, I_n) - g_n(\tilde{S}, I_n) = \beta_n(S - \tilde{S})I_n \le 0, \quad 0 \le S \le \tilde{S}, \quad I_n \ge 0,$$

$$g_n(S, I_n) - g_n(\tilde{S}, I_n) = \beta_n(S - \tilde{S})I_n = 0, \quad I_n > 0, \quad \Longrightarrow \quad S = \tilde{S},$$

$$0 < \frac{g_n(\tilde{S}, I_n)}{\psi(I_n)} = \frac{\beta_n \tilde{S}}{Q_n} < \infty, \quad I_n > 0;$$

(A2): For $j, n \in \{1, \ldots, 5\}$, we have

$$0 \le \frac{\omega_{j,n}(I_n)}{\psi(I_n)} = \frac{\sigma_{j,n}}{Q_n} < \infty, \quad I_n > 0;$$

(B1): For $S \ne S^*$,

$$(\chi(S) - \chi(S^*))(\varphi(S) - \varphi(S^*)) = -\mu(S - S^*)^2 < 0;$$

(B2): For $I_n > 0$, $n = 1, \ldots, 5$, and $0 \le S \le \tilde{S}$,

$$\left(\frac{g_n(S, I_n)}{\varphi(S)} - \frac{g_n(S^*, I_n^*)}{\varphi(S^*)} \right) \left(\frac{g_n(S, I_n)}{\varphi(S)\psi_n(I_n)} - \frac{g_n(S^*, I_n^*)}{\varphi(S^*)\psi_n(I_n^*)} \right) =$$

$$\beta_n(I_n - I_n^*) \left(\frac{\beta_n}{Q_n} - \frac{\beta_n}{Q_n} \right) = 0;$$

(B3): For $I_n > 0$, $n = 1, \ldots, 5$, and for each pair $j, n \in \{1, \ldots, 5\}$,

$$(\omega_{j,n}(I_n) - \omega_{j,n}(I_n)^*) \left(\frac{\omega_{j,n}(I_n)}{\psi_n(I_n)} - \frac{\omega_{j,n}(I_n)^*}{\psi_n(I_n^*)} \right) =$$

$$\sigma_{j,n}(I_n - I_n^*) \left(\frac{\sigma_{j,n}}{Q_n} - \frac{\sigma_{j,n}}{Q_n} \right) = 0;$$

(B4): All the functions $g_n(S, I_n)$, $\psi_n(I_n)$, $\omega_{j,n}(I_n)$, with $j, n = 1, \ldots, 5$, and $\sigma_{j,n} \neq 0$ are strictly monotone with respect to I_n.

Let us finally define the weight matrix M of the infection-transfer graph G of model (4) (see Fig. 11), as $M = (m_{j,n})$, where $m_{1,n} = \omega_{1,n}(I_n^*) + g_n(S^*, I_n^*)$, $n = 1, \ldots, 5$, while $m_{j,n} = \omega_{j,n}(I_n^*)$, $n = 1, \ldots, 5$, for $j = 2, \ldots, 5$. Substituting the expressions of the functions $g_n(S^*, I_n^*)$, $\omega_{j,n}(I_n^*)$, $j, n = 1, \ldots, 5$, we have

$$M = \begin{bmatrix} \beta_1 S^* I_1^* & \beta_2 S^* I_2^* & \beta_3 S^* I_3^* & \beta_4 S^* I_4^* & \beta_5 S^* I_5^* \\ \theta_1 I_1^* & 0 & 0 & 0 & 0 \\ 0 & \theta_2 I_2^* & 0 & 0 & \xi I_5^* \\ 0 & 0 & \theta_3 I_3^* & 0 & 0 \\ 0 & \delta_2 I_2^* & \delta_3 I_3^* & \delta_4 I_4^* & 0 \end{bmatrix}. \tag{38}$$

As the the weighted graph (M, G) of the model (4) is strongly connected, the matrix M results to be irreducible.

On the basis of the properties given above, Theorems 4.1 and 5.1 in [15] hold in our case, guaranteeing that the disease-free equilibrium is globally asymptotically stable for $R \leq 1$ and unstable for $R > 1$, while the endemic equilibrium is unique and also asymptotically stable when $R > 1$ (R is the reproduction number defined in Section 5.1).

However, for the completeness of our study, we report here some details of the proof of Theorem 5.2 given in Section 5.1. As suggested in [15], we consider the following general Lyapunov function

$$L(S, I_1, \ldots, I_5) = c_1 \int_{S^*}^{S} \frac{\varphi(\tau) - \varphi(S^*)}{\varphi(\tau)} d\tau + \sum_{n=1}^{5} c_n \int_{I_n^*}^{I_n} \frac{\psi(\tau) - \psi(I_n^*)}{\psi(\tau)} d\tau. \tag{39}$$

Recalling that in our case the removal rates $\psi_n(I_n)$ are equal to $Q_n I_n$, $n = 1, \ldots, 5$, for the particular choice $\varphi(S) = S$ the general function (39) becomes the function given in (25). Then, we choose the coefficient c_n as the cofactor of the n-th diagonal entry of the algebraic Laplacian
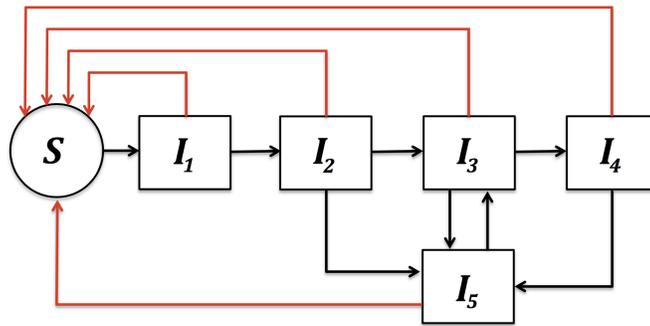

Figure 11: Infection-transfer graph G of model (4). Transfers of individuals between compartments, black arcs; infections, red arcs.

26.

matrix of M defined as

$$\mathcal{L}(M) \;=\; \mathrm{diag}\left(\sum_{n=1}^{5} m_{1,n},\ldots,\sum_{n=1}^{5} m_{5,n}\right) - M = \tag{40}$$

$$\begin{bmatrix}
\sum_{n=2}^{5}\beta_n S^* I_n^* & -\beta_2 S^* I_2^* & -\beta_3 S^* I_3^* & -\beta_4 S^* I_4^* & -\beta_5 S^* I_5^* \\
-\theta_1 I_1^* & \theta_1 I_1^* & 0 & 0 & 0 \\
0 & -\theta_2 I_2^* & \theta_2 I_2^* + \xi I_5^* & 0 & -\xi I_5^* \\
0 & 0 & -\theta_3 I_3^* & \theta_3 I_3^* & 0 \\
0 & -\delta_2 I_2^* & -\delta_3 I_3^* & -\delta_4 I_4^* & \sum_{n=2}^{4}\delta_n I_n^*
\end{bmatrix}. \tag{41}$$

It can be easily verified that the five cofactors of $\mathcal{L}(M)$ are given by (29), (30). By inferring the relation $c_2 = (\sum_{n=2}^{5} B_n/\Theta_1)c_1$ from equations (29), the function (28) can be rewritten as

$$\dot{L}(S, I_1,\ldots, I_5) = T'(S, I_1,\ldots, I_5) + T''(S, I_1,\ldots, I_5), \tag{42}$$

where

$$T'(S, I_1,\ldots, I_5) = c_1\left((\mu S^* + B_1)\left(2 - s - \frac{1}{s}\right) + B_2\left(3 - \frac{si_2}{i_1} - \frac{1}{s} - \frac{i_1}{i_2}\right)\right), \tag{43}$$

and

$$T''(S, I_1,\ldots, I_5) =$$
$$c_1\sum_{n=3}^{5} B_n\left(3 - \frac{si_n}{i_1} - \frac{1}{s} - \frac{i_1}{i_2} - i_2 + i_n\right) +$$
$$c_3\left(\theta_2 I_2^*\left(1 - \frac{i_2}{i_3} - i_3 + i_2\right) + \xi I_5^*\left(1 - \frac{i_5}{i_3} - i_3 + i_5\right)\right) + c_4\left(\theta_3 I_3^*\left(1 - \frac{i_3}{i_4} - i_4 + i_3\right)\right) + \tag{44}$$
$$c_5\left(\delta_2 I_2^*\left(1 - \frac{i_2}{i_5} - i_5 + i_2\right) + \delta_3 I_3^*\left(1 - \frac{i_3}{i_5} - i_5 + i_3\right) + \delta_4 I_4^*\left(1 - \frac{i_4}{i_5} - i_5 + i_4\right)\right).$$

Since from the arithmetic-mean/geometric-mean inequality we have $(2 - s - 1/s) \leq 0$ and $(3 - si_2/i_1 - 1/s - i_1/i_2) \leq 0$, the function (43) is non-positive. In order to prove the non-positiveness of the second term of the function (42), we directly substitute in Eq. (44) the expressions of c_1, c_3, c_4 and c_5 given in (29). Then, collecting the terms with respect to B_n,

$n = 3, 4, 5$, we obtain

$$T''(S, I_1, \ldots, I_5) =$$

$$B_3\left(\Theta_1\Theta_3\left(\Theta_2\sum_{n=2}^{4}\Delta_n\left(4 - \frac{si_3}{i_1} - \frac{1}{s} - \frac{i_1}{i_2} - \frac{i_2}{i_3}\right) + \Xi_5\Delta_2\left(5 - \frac{si_3}{i_1} - \frac{1}{s} - \frac{i_1}{i_2} - \frac{i_5}{i_3} - \frac{i_2}{i_5}\right) + \right.\right.$$

$$\left.\left.\Xi_5\Delta_3\left(2 - \frac{i_5}{i_3} - \frac{i_3}{i_5}\right) + \Xi_5\Delta_4\left(3 - \frac{i_5}{i_3} - \frac{i_3}{i_4} - \frac{i_4}{i_5}\right)\right)\right) +$$

$$B_4\left(\Theta_1\Theta_3\left(\Theta_2\sum_{n=2}^{4}\Delta_n\left(5 - \frac{si_4}{i_1} - \frac{1}{s} - \frac{i_1}{i_2} - \frac{i_2}{i_3} - \frac{i_3}{i_4}\right) + \Xi_5\Delta_2\left(6 - \frac{si_4}{i_1} - \frac{1}{s} - \frac{i_1}{i_2} - \frac{i_5}{i_3} - \frac{i_3}{i_4} - \frac{i_2}{i_5}\right) + \right.\right.$$

$$\left.\left.\Xi_5\Delta_3\left(2 - \frac{i_5}{i_3} - \frac{i_3}{i_5}\right) + \Xi_5\Delta_4\left(3 - \frac{i_5}{i_3} - \frac{i_3}{i_4} - \frac{i_4}{i_5}\right)\right)\right) +$$

$$B_5\left(\Theta_1\Theta_3\left(\Theta_2\Delta_2\left(4 - \frac{si_5}{i_1} - \frac{1}{s} - \frac{i_1}{i_2} - \frac{i_2}{i_5}\right) + \Theta_2\Delta_3\left(5 - \frac{si_5}{i_1} - \frac{1}{s} - \frac{i_1}{i_2} - \frac{i_2}{i_3} - \frac{i_3}{i_5}\right) + \right.\right.$$

$$\Theta_2\Delta_4\left(6 - \frac{si_5}{i_1} - \frac{1}{s} - \frac{i_1}{i_2} - \frac{i_2}{i_3} - \frac{i_3}{i_4} - \frac{i_4}{i_5}\right) + \Xi_5\Delta_2\left(4 - \frac{si_5}{i_1} - \frac{1}{s} - \frac{i_1}{i_2} - \frac{i_2}{i_5}\right) +$$

$$\left.\left.\Xi_5\Delta_3\left(2 - \frac{i_5}{i_3} - \frac{i_3}{i_5}\right) + \Xi_5\Delta_4\left(3 - \frac{i_5}{i_3} - \frac{i_3}{i_4} - \frac{i_4}{i_5}\right)\right)\right).$$

$$(45)$$

From (45) it is easy to deduce that $T''(S, I_1, \ldots, I_5) \leq 0$ since, exploiting again the arithmetic-mean/geometric-mean inequality, all the polynomials in the brackets result to be actually non-positive. With this last statement we can conclude that $\dot{L}(S, I_1, \ldots, I_5) \leq 0$.

Finally, in order to prove the asymptotic stability of E_{en}, we need to verify that $\dot{L}(S, I_1, \ldots, I_5) = 0$ if and only if $(S, I_1, \ldots, I_5) \equiv (S^*, I_1^*, \ldots, I_5^*)$. Indeed, if $\dot{L}(S, I_1, \ldots, I_5) = 0$ it follows that all the polynomials in the brackets of equations (43) and (45) are equal to zero. Then, it is easy to obtain that each point satisfying $\dot{L}(S, I_1, \ldots, I_5) = 0$ is such that

$$S = S^*, \qquad i_n = \lambda, \quad n = 1, \ldots, 5, \tag{46}$$

where λ is a positive constant. In other words, each solution satisfying $\dot{L}(S, I_1, \ldots, I_5) = 0$ is a time-invariant solution identified by $S(t) = S^*$, $I_n(t) = \lambda I_n^*$, $n = 1, \ldots, 5$. Consequently, from the equation of $\dot{S}$ in (4) we obtain

$$0 = \Lambda - \mu S^* - \lambda\sum_{n=1}^{5}\beta_n I_n^* S^*. \tag{47}$$

Since the same equation holds for the endemic equilibrium with $\lambda = 1$, we deduce that Eq. (47) can be verified only for $\lambda = 1$, because of its linearity with respect to λ. So, we can conclude $\dot{L}(S, I_1, \ldots, I_5) = 0 \Leftrightarrow (S, I_1, \ldots, I_5) \equiv (S^*, I_1^*, \ldots, I_5^*)$.