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HIV treatment planning on a case-by-case basis

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Abstract—This study presents a mathematical modeling approach to the planning of HIV therapies on an individual basis. The model replicates clinical data from typical-progressors to AIDS for all stages of the disease with good agreement. Clinical data from rapid-progressors and long-term non-progressors is also matched by estimation of immune system parameters only. The ability of the model to reproduce these phenomena validates the formulation, a fact which is exploited in the investigation of effective therapies. The therapy investigation suggests that, unlike continuous therapy, structured treatment interruptions (STIs) are able to control the increase in both the drug-sensitive and drug-resistant virus population and, hence, prevent the ultimate progression from HIV to AIDS. The optimization results further suggest that even patients characterised by the same progression type can respond very differently to the same treatment and that the latter should be designed on a case-by-case basis. Such a methodology is presented here.

Keywords—AIDS, chemotherapy, mathematical modeling, optimal control, progression.

I. Introduction

DESPITE the impressive amount of work in HIV research there are as yet no effective treatment strategies that prevent the ultimate progression from HIV to AIDS and death. Mathematical modeling can synthesize existing knowledge and provide a theoretical framework for the interpretation of existing paradigms. Furthermore, mathematical models can serve as a powerful tool in the quest for computing optimal treatment strategies due to their ability to estimate the patient's response to therapy [1].

It is important to validate any modelling attempt by using data from clinical trials or experimental studies. This has not been considered in most modeling work reported to date ([2]-[4]) yet is obviously essential in order to ensure that the model predictions replicate real phenomena. In addition, many studies did not consider the drug-resistant virus population ([2], [5]). The emergence of such a strain is known to be a key factor in the failure of current strategies and any proposed therapies that do not take this phenomenon into account are likely to be misleading. Furthermore, most studies [3] reported optimized strategies over very short treatment durations. Unless the goal of the study is to eradicate the virus or to achieve immunological control after cessation of treatment (this has as yet been proven to be very difficult to achieve due to the replication of virus in macrophages and long-lived cells ([6], [7]), optimal control studies should aim in designing a strategy which increases the long-term treatment benefit. Investigating short horizons might lead to results which are optimal over that short horizon but are not necessarily optimal in the long-term.

Many studies to date ([1], [2], [5]) considered the effect of treatment through an efficacy term. Different drugs, however, are associated with varied efficacies in the body as well as with different side-effects, hence, treatment planning oughts to be drug-specific. Krakovska and Wahl [3] produced optimal strategies by considering the varied efficacies of different drugs, however, in their formulation all drugs carried a similar toxicity rating. This is rarely true and a side-effect index which takes into account the different toxicities associated with different drugs has to be considered. Lastly, no two individuals respond to infection and treatment in quite the same and a methodology which allows for patient-specific planning needs to be investigated.

We present here a mathematical model which considers all cell populations known to play a key role in HIV infection, including the drug-resistant virus population. The model is compared to literature-reported clinical data from different patients for the entire trajectory of the disease and used as a tool for the planning of treatment. The methodology proposed here allows for the formulation of long-term patient-specific drug-specific strategies. The paper is ordered as follows: Section I presents a mathematical modeling approach to the investigation of HIV treatment strategies, Section II presents the analysis of the optimal control results and a methodology for the formulation of therapy on an individual basis, Section III involves a discussion on the findings, and Section IV outlines the most important conclusions of this study.

II. Methods

A. HIV dynamics

HIV infection can be characterised as a disease of the immune system, with progressive depletion of defensive cells, resulting in immunosuppression. Viruses cannot reproduce without the aid of living cells. HIV can infect a number of cells in the body, however, its main target are the CD4+ T-cells. HIV replicates inside infected cells and the newly-produced virus can now infect more cells. CD4+ T-cells are vital as they help facilitate the body's response to many common but potentially fatal infections. The HIV life cycle directly or indirectly causes a reduction in the number of these cells, rendering the body's immune system unable to defend itself against these infections. The key phenomena in the HIV infection cycle are illustrated in Fig. 1.

Once infected, the patient experiences a rapid decrease in the number of CD4+ T-cells, following a rapid increase in the virus population. The immune system (CTLs and macrophages) responds by killing infected cells and virus particles, causing a rapid increase in the number of T-cells. During

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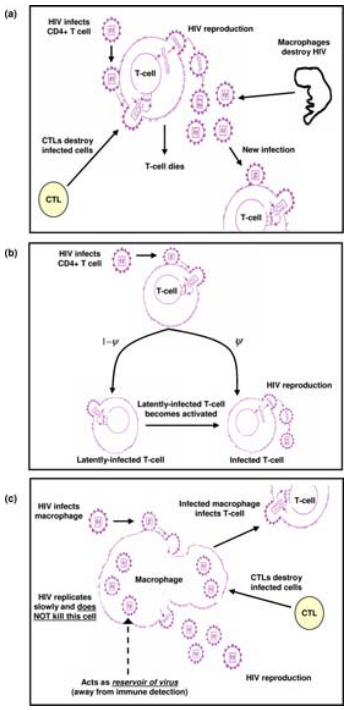

Fig. 1. Key phenomena during the course of HIV infection in (a) CD4+ T-cells, (b) latently-infected CD4+ T-cells, and (c) macrophages. Once infected a proportion $1-\psi$ of CD4+ T-cells passes into the latently-infected cell population. Reproduced from [9].

this time the virus population experiences a rapid depletion. A period of almost eight years follows (often referred to as the asymptomatic stage or latency) whereby CD4+ T-cells experience a constant but slow depletion. The virus infects more and more cells and thus slowly increases in number. After about eight years the immune system collapses and the virus population experiences an exponential growth. On the other hand, uninfected T-cells deplete at a high rate, crossing the 200 mm^{-3} line which marks the "progression to AIDS" period. Once patients are detected with AIDS, they survive for about one more year as suggested by [8]. Furthermore, once infected a proportion $1-\psi$ of CD4+ T-cells (Fig. 1(b)) passes into the latently-infected cell population. These latently-infected cells may be activated after a long time, and start reproducing virus.

During the course of HIV infection macrophages are also infected (Fig. 1(c)). The virus replicates slowly inside these cells and, unlike CD4+ T-cells, the macrophages are not killed but continue to accommodate more virus and protect it against immune responses and drugs. Also of importance is the fact that infected macrophages appear to be able to cause apoptosis of CD4+ T-cells [10]. Clinical studies [11] have suggested that during the late stages of the disease most virus comes from infected macrophages, hence the exponential rise.

B. HIV model

The following components are considered: T, uninfected T-cells; T_1, T-cells infected by wild-type virus (drug-sensitive); T_2, T-cells infected by mutated virus (drug-resistant); T_{L1}, latently-infected T-cells infected by wild-type virus; T_{L2}, latently-infected T-cells infected by mutated virus; V_1, wild-type virus (drug-sensitive); and V_2, mutated virus (drug-resistant). The model also considers the uninfected and infected macrophage populations, M, M_1 and M_2, respectively, as well as the cytotoxic T-lymphocyte population, CTL. The governing set of differential equations is given by (1)-(11).

$$\frac{dT}{dt} = s_1 + \frac{p_1(V_1+V_2)T}{V_1+V_2+S_1} - (1-u_1)(k_1V_1+k_2M_1)T - \varphi(k_1V_2+k_2M_2)T + rT(1-\frac{T+T_1+T_2+T_{L1}+T_{L2}}{T_{max}}) - \delta_1 T \quad (1)$$

$$\frac{dT_1}{dt} = (1-u_1)\psi(k_1V_1+k_2M_1)T + \alpha_1 T_{L1} - \delta_2 T_1 - k_3 T_1 CTL \quad (2)$$

$$\frac{dT_2}{dt} = \psi\varphi(k_1V_2+k_2M_2)T + \alpha_1 T_{L2} - \delta_2 T_2 - k_3 T_2 CTL \quad (3)$$

$$\frac{dT_{L1}}{dt} = (1-u_1)(1-\psi)(k_1V_1+k_2M_1)T - \alpha_1 T_{L1} - \delta_3 T_{L1} \quad (4)$$

$$\frac{dT_{L2}}{dt} = (1-\psi)\varphi(k_1V_2+k_2M_2)T - \alpha_1 T_{L2} - \delta_3 T_{L2} \quad (5)$$

$$\frac{dM}{dt} = s_2 + \frac{p_2(V_1+V_2)M}{V_1+V_2+S_2} - (1-f_1u_1)k_4V_1M - \varphi k_4V_2M - \delta_4 M \quad (6)$$

$$\frac{dM_1}{dt} = (1-f_1u_1)k_4V_1M - \delta_5 M_1 - k_5 M_1 CTL \quad (7)$$

$$\frac{dM_2}{dt} = \varphi k_4V_2M - \delta_5 M_2 - k_5 M_2 CTL \quad (8)$$

$$\frac{dCTL}{dt} = s_3 + k_6(T_1+T_2)CTL + k_7(M_1+M_2)CTL - \delta_6 CTL \quad (9)$$

$$\frac{dV_1}{dt} = (1-u_2)(1-\mu)k_8T_1 + (1-f_2u_2)(1-\mu)k_9M_1 + \mu\varphi k_8T_2 + \mu\varphi k_9M_2 - (k_{10}T+k_{11}M)V_1 - k_{12}V_1M - \delta_7 V_1 \quad (10)$$

$$\frac{dV_2}{dt} = (1-\mu)\varphi k_8T_2 + (1-\mu)\varphi k_9M_2 + (1-u_2)\mu k_8T_1 + (1-f_2u_2)\mu k_9M_1 - (k_{10}T+k_{11}M)V_2 - k_{12}V_2M - \delta_7 V_2 \quad (11)$$

(1) characterises the changes in the uninfected T-cell population, T. The first two terms on the RHS of (1) represent the sources of new T-cells. They incorporate cells from the thymus, bone marrow, and general production. It is assumed that there exists a constant thymic source, s_1, as well as a proliferation term due to an immune response. T-cells have finite lifespans; the average of which is $1/\delta_1$, where δ_1 is the death rate of the uninfected T-cells. The last two terms on the RHS of (1) represent the infection of T-cells by both virus and infected macrophages (drug-sensitive and drug-resistant strain). Constant rates of infectivity k_1 and k_2 are assumed. Consideration of macrophages is regarded essential since this population plays a vital role in HIV progression. The logistic term in (1) does not allow the T-cell population to exceed a maximum concentration, T_{max} following antiretroviral treatment ([12],[13]).

(2)-(5) describe changes in the infected and latently-infected T-cell populations, T_1, T_2, T_{L1}, T_{L2}. The first term on the RHS of the equations represents the increase in number of infected cells. Once infected, a proportion of T-cells, ψ, passes into the infected T-cell population, whereas a proportion $1-\psi$ passes into the latently-infected T-cell population. These latently-infected cells might become activated after a long time and start reproducing virus. This activation is represented through

the $\alpha_1 T_{L1}$ and $\alpha_1 T_{L2}$ terms in (2)-(5). Infected cells are lost by such processes such as natural death and immune responses. The rate at which CTLs kill infected T-cells is given by k_3 in (2)-(3).

The population of macrophages increases in terms of the constant source of new cells, s_2, and its increase due to the immune response (6). The latter term depends on the number of virus particles and the increase rate, p_2. According to [10], when T-cells signal macrophages that the virus is non-self (*i.e.*, an 'invader'), the latter divide and become more aggressive. Thus, it was considered essential to include this behaviour in the model. Macrophages are lost through infection by virus at a rate of k_4, and through natural death at a rate of δ_4. In (7) and (8) the gain terms carry over from the loss terms in (6). Infected macrophages (both strains) are lost to natural death and to immune responses. The rate at which CTLs kill infected macrophages is given by k_5.

The rate of change of CTLs is given by (9). These cells are generated at a constant rate, s_3, and proliferate with a rate described by rate constants, k_6 and k_7, proportional to the current amount of the same infected T-cells and infected macrophages, respectively. CTLs die at a rate δ_6.

(10) and (11) describe the rate of change in the drug-sensitive (V_1) and drug-resistant (V_2) virus population, respectively. These populations increase due to production of virus from drug-sensitive and drug-resistant infected T-cells and macrophages, respectively. For example, the amount of V_2 produced from T_2 and M_2 is given by $(1-\mu)k_8 T_2$ and $(1-\mu)k_9 M_2$, respectively, where k_8 and k_9 are the rates of production per unit time in T-cells and macrophages. The amount of V_2 produced from T_1 and M_1 is given by $\mu k_8 T_1$ and $\mu k_9 M_1$, respectively, where μ represents the percentage of virus mutation (V_1 to V_2, and vice versa). Virus is lost through the terms $k_{10} V_i T$ and $k_{11} V_i M$, effectively accounting for the virus lost when infecting T-cells and macrophages without producing new virus, *e.g.*, as a result of the infected cell's natural death or through the action of CTLs. Virus is also lost through natural death ($\delta_7 V_i$) as well as through an immune response ($k_{12} V_i M$).

Viral mutations are accounted in the model via the parameter μ, which represents the probability of a mutation per replication cycle (V_1 to V_2, and vice-versa). This approach has also been used in other studies ([14], [15]) and takes indirectly into account the mutations occuring in both the transcription and production stage of the replication cycle. The reduced fitness of V_2 in terms of infecting and replicating capacity is considered in the model equations above through parameter φ.

Parameters u_1 and u_2 ($u_1, u_2 \in [0,1]$, with 0 and 1 indicating no treatment and full treatment, respectively) represent the efficacy of reverse transcriptase inhibitors (RTI) and protease inhibitors (PI), respectively. RTIs inhibit the infection of T-cells and macrophages by virus whereas the PIs inhibit the production of infectious virus from already infected cells. It is important to note that these drugs have no effect on the resistant virus population. Treatment on macrophages is not as effective as that on T-cells hence, the term $f_i u_i$ [2]. Estimation of drug efficacies in the body requires use of a pharmacokinetic model which is described in Appendix A.

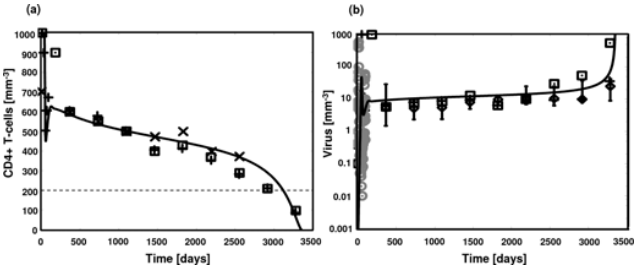

Fig. 2. Concentration-time profiles for (a) CD4+ T-cell and (b) virus for an untreated typical-progressor to AIDS. Model predictions from Hadjiandreou *et al.* [23]. Comparison with clinical data from the studies by [18] (+), [24] (○), [25] (◇), [19] (×), and [20] (□). Dotted line marks progression to AIDS.

TABLE I
PARAMETER VALUES USED IN THE MODEL. UNLESS OTHERWISE STATED, BEST FIT VALUES ESTIMATED (EST.) FROM CLINICAL DATA OF T-CELLS ([18], [19], [20]) WHEN NO TREATMENT IS USED.

Parameter	Value	Source	Literature	Units
s_1	10	[13]	$5-36$	$\text{mm}^{-3}\text{d}^{-1}$
s_2	0.15	[13]	$0.03-0.15$	$\text{mm}^{-3}\text{d}^{-1}$
s_3	5	Est.	–	$\text{mm}^{-3}\text{d}^{-1}$
p_1	0.16	Est.	$0.01-5$	d^{-1}
p_2	0.15	Est.	–	d^{-1}
S_1	55.6	Est.	$1-188$	mm^{-3}
S_2	188	Est.	–	mm^{-3}
k_1	$3.87\ \text{x}10^{-3}$	Est.	$10^{-8}-10^{-2}$	mm^3d^{-1}
k_2	$1\ \text{x}10^{-6}$	[13]	10^{-6}	mm^3d^{-1}
k_3	$4.5\ \text{x}10^{-4}$	Est.	$10^{-4}-1$	mm^3d^{-1}
k_4	$5.22\ \text{x}10^{-4}$	Est.	$4.7\text{x}10^{-9}-10^{-3}$	mm^3d^{-1}
k_5	$3\ \text{x}10^{-6}$	Est.	–	mm^3d^{-1}
k_6	$3.3\ \text{x}10^{-4}$	Est.	$10^{-6}-10^{-3}$	mm^3d^{-1}
k_7	$6\ \text{x}10^{-9}$	Est.	–	mm^3d^{-1}
k_8	$5.37\ \text{x}10^{-1}$	Est.	$2.4\text{x}10^{-1}-5\text{x}10^{2}$	d^{-1}
k_9	$2.85\ \text{x}10^{-1}$	Est.	$5\text{x}10^{-3}-3\text{x}10^{2}$	d^{-1}
k_{10}	$7.79\ \text{x}10^{-6}$	Est.	$10^{-8}-10^{-2}$	mm^3d^{-1}
k_{11}	$1\ \text{x}10^{-6}$	Est.	$4.7\text{x}10^{-9}-10^{-3}$	mm^3d^{-1}
k_{12}	$4\ \text{x}10^{-5}$	Est.	–	mm^3d^{-1}
δ_1	0.02	[13]	$0.01-0.02$	d^{-1}
δ_2	0.28	Est.	$0.24-0.7$	d^{-1}
δ_3	0.05	Est.	$0.02-0.069$	d^{-1}
δ_4	$5\ \text{x}10^{-3}$	[13]	0.005	d^{-1}
δ_5	$5\ \text{x}10^{-3}$	[13]	0.005	d^{-1}
δ_6	0.015	[21]	$0.015-0.05$	d^{-1}
δ_7	2.39	[13]	$2.39-13$	d^{-1}
α_1	$3\ \text{x}10^{-4}$	Est.	–	d^{-1}
ψ	0.97	Est.	$0.93-0.98$	–
φ	0.9	[22]	$0.1-0.9$	–
r	0.03	[13]	0.03	d^{-1}
T_{max}	1500	[13]	$1500-2000$	mm^{-3}
μ	0.001	[14]	$3\text{x}10^{-5}$-$1\text{x}10^{-3}$	–
f_i	0.34	[2]	0.34	–

In specifying model parameters and initial conditions for the model, estimated values were generated from clinical data of T-cell dynamics of typical-progressors when no therapy is used. This was done using a least-squares method code written in *Mathematica 5.1*^{TM} [16]. Some parameter values were taken directly from the literature. Estimates of parameter values are given in Table I. Furthermore, $T(0) = 1000$ mm^{-3}, $M(0) = 30$ mm^{-3}, $V_1(0) = 0.001$ mm^{-3} [13], and $CTL(0) = 333$ mm^{-3} [17]. It should be noted that the initial concentrations for the infected populations and V_2 were set to 0.

Fig. 2 presents data from five clinical studies representing the typical progression of the disease, with the results of the model given for direct comparison. The predictions for the T-cells and virus populations show good agreement with clinical data for HIV-infected patients during the same time period. It is important to note that although clinical data for the T-cells alone were used in the parameter estimation, the model is able to replicate clinical data for the virus population as well, including the exponential rise of the virus towards the end-stages of the disease. This further validates the modeling work in this study.

C. Rapid-progressors and long-term non-progressors

In this section, we investigate the ability of the model to replicate clinical data from other progressors to AIDS, namely rapid-progressors (RPs) and long-term non-progressors (LTNPs). RPs are those patients whose T-cell levels decrease below the threshold of AIDS after approximately 3-5 years [5]. These constitute a small proportion (10% [26]) of infected individuals. The majority of patients progress to AIDS within 8-10 years after initial infection and are known as typical-progressors (see above). LTNPs are a small proportion (10-17% [26]) of the infected population who evade the typical progression to AIDS without the help of therapy for as long as 15-20 years ([5], [27]). The differences in the rate of progression between individuals has been suggested to be based on factors such as immune system's status, age, and genetic profile ([5], [28]). Here, the parameters associated with the immune system alone are estimated using a least-squares code written in *Mathematica 5.1*^{TM}; namely, the action of the CTLs (k_3, k_5) and macrophages (k_{12}) on the infected cells and virus, respectively, as well as the increase of uninfected cells (T-cells, macrophages, and CTLs) as part of the immune response ($p_1, p_2, S_1, S_2, k_6,$ and k_7). The estimated parameter values are listed in Table II with plots depicting cell population concentration-time profiles for both RPs and LTNPs shown in Fig. 3. Clinical data for T-cell dynamics from RPs and LTNPs have been plotted alongside model results for comparison.

It is important to note the effect of the immune system parameters on the degree of progression to AIDS. For the RP, a reduction in these parameters (*e.g.*, 12% decrease of proliferation rate of CTLs, k_6 and k_7) results in a weaker immune response (Fig. 3(c)), hence, an increased virus load

TABLE II
PARAMETER VALUES USED IN THE MODEL FOR A RP AND A LTNP. THE VALUES OF THE REMAINING PARAMETERS ARE SIMILAR TO THE ONES FOR THE TYPICAL-PROGRESSOR'S CASE (TABLE I).

Parameter	RP	Typical-progressor	LTNP	Units
p_1	0.13	0.16	0.2	d^{-1}
p_2	0.1365	0.15	0.1638	d^{-1}
S_1	50.0	55.6	55.6	mm^{-3}
S_2	169.2	188	188	mm^{-3}
k_3	$3.96\ x10^{-4}$	$4.5\ x10^{-4}$	$9.9\ x10^{-4}$	mm^{-3}
k_5	$2.64\ x10^{-6}$	$3\ x10^{-6}$	$6.6\ x10^{-6}$	mm^{-3}
k_6	$2.9\ x10^{-4}$	$3.3\ x10^{-4}$	$3.63\ x10^{-4}$	mm^{-3}
k_7	$5.28\ x10^{-9}$	$6\ x10^{-9}$	$6.6\ x10^{-9}$	mm^{-3}
k_{12}	$3.52\ x10^{-5}$	$4\ x10^{-5}$	$4.4\ x10^{-5}$	mm^{-3}
r	0.03	0.03	0.072	d^{-1}

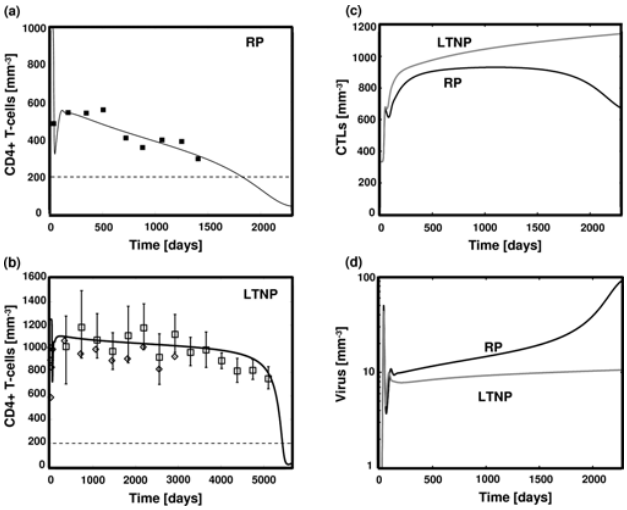

Fig. 3. Concentration-time profiles for T-cells (a-b), CTLs (c), and total virus (d) for an untreated RP and LTNP. Comparison with clinical data from the clinical studies by [29] (■), [18] (◊), and [30] (□). The data from [30] (□) involved 7 patients, hence the mean and standard error bars. Dotted line marks progression to AIDS.

(Fig. 3(d)) and a more rapid decline in the T-cell count (Fig. 3(a)). Model results for T-cell dynamics show good agreement with clinical data from one patient. For the LTNP case, an increase in the immune system parameters (*e.g.*, 10% increase in k_6 and k_7) results in a stronger immune response (Fig. 3(c)), hence, a reduced virus load (Fig. 3(d)) and a considerably slower depletion of T-cells (Fig. 3(b)). It is worth noting the difference in the life expectancies of the three types of progressors (RP: 6 years, typical: 9.5 years, LTNP: 15.5 years). Model results for the T-cell dynamics have been compared with clinical data from patients displaying LTNP characteristics with good agreement. This match of clinical data further validates the modeling work in this study, which is able to replicate the dynamics of different types of progressors. This has been achieved by estimating only the parameters associated with the immune system response. The performance of the immune system has been suggested ([5], [24]) to be one of the main factors determining the degree of progression to AIDS, and the ability of the model to reproduce some features of this phenomenon further validates its application.

D. Drug Related side-effects

An optimal strategy clearly involves the successful control of the disease. Another parameter which has to be considered in the formulation of treatment strategies, however, is the intensity of the drug-related side-effects. Neglecting this might prove fatal to the patient. The relationship between antiretroviral drugs and their side-effects is well documented [31]. Table III summarises the observed side-effects as a result of three widely used antiretroviral drugs at standard dosage (one PI, RDV, and two RTIs, 3TC and ZDV). More specifically, the table summarises the observed frequency of the side-effect within a population as well as its relative magnitude. The latter is clearly subjective, *e.g.*, "chills" should be less

undesirable than an “increase in blood sugar” or ”diaorrhea”. A drug-specific side-effect index formulation in an attempt to investigate the impact of side-effects in the optimal design of treatment strategies is presented in Appendix B.

III. Results and discussion

Here, patient and drug-specific optimal treatment profiles for HIV-infected patients employing a widely used drug regime (RDV, 3TC, ZDV) and drug concentrations as controls are generated using *gPROMS 3.0.3* [33]. In this work, an optimal treatment is one that prolongs progression to AIDS so as to evade opportunistic infections, maintains a high CD4+ T-cell count, as well as reduces the impact of drug-associated side-effects.

A. Structured treatment interruptions

Hadjiandreou *et al.* [9] involved the investigation of treatment strategies using drug efficacies as controls. Both continuous therapy and STIs were considered and the results suggested that, unlike continuous therapy, STIs are very effective in controlling disease progression. It was suggested that the key to the successful implementation of STI therapy, which is not as yet included in antiretroviral guidelines, is the optimal management of the magnitude and frequency of treatment interruptions in an attempt to fascilitate the interplay between the drug-sensitive and drug-resistant virus strains. In this way, neither the sensitive nor the resistant strain increase and disease progression can be controlled as a result.

That work is extended here by the formulation of a dynamic optimization problem of STI therapy for the case of a typical-progressor (see Fig. 2 and Table I) using the drug-specific model presented earlier. The optimal control problem takes the form of OCP1:

OCP1

$$\max_{C_1,\, C_2,\, C_3} J(t_f,\, \mathbf{C})$$

$$\text{s. t.} \qquad J(t_f,\, \mathbf{C}) = \int_{t_0}^{t_f} [A_1 T - A_2 S_e]\ \mathrm{dt} \qquad (12)$$
$$\dot{\mathbf{x}} = f(t,\, \mathbf{x},\, \mathbf{C}),$$
$$T \geqslant T_{AIDS},$$
$$t \in [t_0,\, t_f]$$

where $\dot{\mathbf{x}} = f(t, \mathbf{x}, \mathbf{C})$ represents the governing set of equations ((1)-(11), (13)-(18)), $t \in [t_0, t_f]$ sets the finite horizon of the optimization, and T_{AIDS} defines the condition for the undesirable transition from HIV to full-blown AIDS. The benefit of treatment is based on the maximisation of T-cells and the minimisation of the severity of side-effects associated with the drug regime over the treatment horizon. A fixed life expectancy of 10,000 days ($\backsim$28 years) after initial infection is assumed. Bearing in mind that current treatment strategies extend life expectancy to a maximum of around 19 years depending on the type of patient and drug regime used ([34]-[36]), it is believed that an estimated life expectancy of $\sim$28 years after initial infection is a realistic target to consider.

Like other problems of discontinuous nature, optimization of the pharmacokinetics during multiple doses adds further complexity to the problem. The latter is already quite complicated due to the highly non-linear nature of the system of equations involved. In order to reduce the complexity associated with modeling pharmacokinetics in the optimization, the concentration of drug i during dosage interval τ is modelled as following an average concentration during that time interval. Moreover, the treatment levels are fixed during the optimization in an attempt to reduce the complexity further. Administration of fixed drug dosages over treatment intervals also helps compliance from clinicians and patients.

Treatment initiation occurs at $T < 350$ mm^{-3} (Antiretroviral Guidelines [37]) with fixed values for average C_1, C_2, and C_3 at $[0.0472,\ 0.0205,\ 0.00659]^T$ and $[0.0,\ 0.0,\ 0.0]^T$ during ON and OFF treatment, respectively. Given initiation at $T < 350$ mm^{-3} these values (equivalent to $\mathbf{u} = [0.1, 0.3]^T$) were found (using optimization) to be the minimum concentrations that are able to achieve the target life expectancy of 10,000 days. The ON and OFF periods are allowed to vary between $10 \leqslant ON, OFF \leqslant 150$ days, thereby excluding

TABLE III
Frequencies and estimated relative magnitude of three widely used drugs. Side-effect reported in $> 15\%$ ($\times$)of individuals, $5 - 15\ \%$ ($\square$), $< 5\%$ ($\bullet$), and side-effect not reported in individuals ($+$). Side-effect is considered “strongly undesirable” (***), undesirable (**), and “weakly undesirable” (*).

SIDE-EFFECT	**DRUG**		
Following laboratory tests	**RDV**	**3TC**	**ZDV**
Anemia **	$\bullet$	$\bullet$	$\times$
Leukopenia **	$\bullet$	$\bullet$	$\times$
Neutropenia **	$\bullet$	$\square$	$\times$
Thrombocytopenia **	$\bullet$	$\bullet$	$\bullet$
$\uparrow$ Alkaline Phosphatase **	$\bullet$	$+$	$+$
$\uparrow$ Amylase (pancreas) **	$\bullet$	$\bullet$	$+$
$\uparrow$ Bilirubin (liver) **	$\bullet$	$\bullet$	$\bullet$
$\uparrow$ Cholesterol ***	$\times$	$+$	$+$
$\uparrow$ Creatinine (kidney) **	$\square$	$+$	$+$
$\uparrow$ Glucose (blood sugar) ***	$+$	$+$	$+$
$\uparrow$ Liver functions **	$\square$	$\bullet$	$\times$
$\uparrow$ Triglycerides **	$\times$	$+$	$+$
As symptoms	**RDV**	**3TC**	**ZDV**
Abdominal pain **	$\square$	$\square$	$\times$
Altered taste *	$\times$	$+$	$\square$
Anorexia **	$\square$	$\square$	$\times$
Arthalgia **	$\bullet$	$\square$	$\times$
Chills *	$\bullet$	$\square$	$\times$
Constipation *	$\bullet$	$+$	$\bullet$
Depression *	$\bullet$	$\square$	$\bullet$
Diaorrhea ***	$\times$	$\times$	$\times$
Dizziness **	$\square$	$\square$	$\square$
Fatigue **	$\times$	$\times$	$\square$
Fevers **	$\bullet$	$\square$	$\times$
Headache **	$\square$	$\times$	$\times$
Insomnia *	$\bullet$	$\square$	$\square$
Malaise **	$\square$	$\times$	$\times$
Menstrual irregularities *	$\times$	$+$	$+$
Myalgia (musle pain) **	$\square$	$\square$	$\times$
Nausea ***	$\times$	$\times$	$\times$
Nephrolithiasis **	$+$	$+$	$+$
Neurological symptoms ***	$\square$	$\bullet$	$\bullet$
Neuropathy **	$\bullet$	$\square$	$\bullet$
Pancreatitis ***	$\bullet$	$\square$	$+$
Paresthesia **	$\times$	$+$	$\bullet$
Rash ***	$\bullet$	$\square$	$\times$
Seizures *	$+$	$+$	$+$
Vomiting ***	$\times$	$\square$	$\square$

Reproduced from [31] and [32]

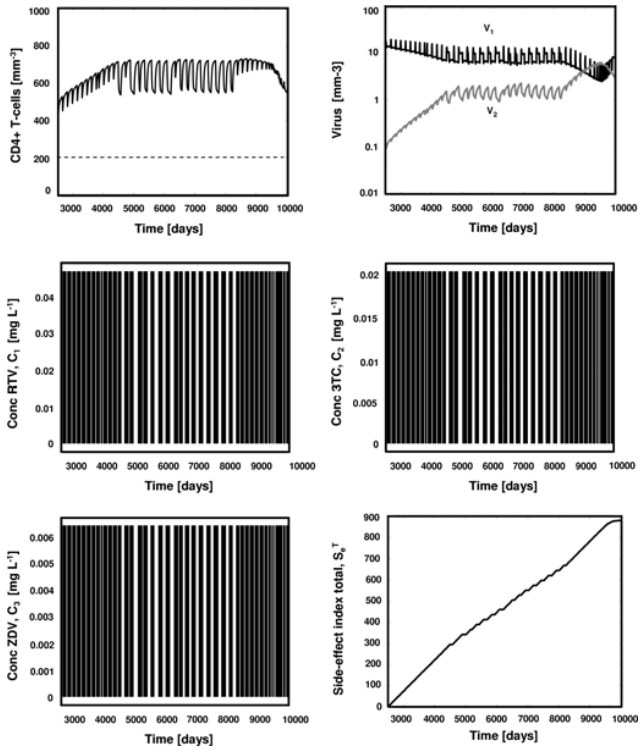

Fig. 4. Optimal control profiles of C_1, C_2, and C_3 for STIs for a treatment-naive typical-progressor. Objective function: $J(t_f,\ \mathbf{u}) = \int_{t_0}^{t_f} [A_1 T - A_2 S_e]$ dt. Initiation of therapy is at $T < 350$ mm^{-3} ($\backsim 2,500$ days after initial infection). Shaded region indicates treatment spell. Dotted line marks progression to AIDS.

extended periods of OFF treatment that could be fatal to the patient ([38], [39]). Since the magnitudes of the T-cell population and the side-effect index are on different scales, weighting values $A_1 = 1$ mm^3 and $A_2 = 1,000$ are used. The optimization solution is sensitive to an increase in A_2, with low administration of both drugs as A_2 increases (results not shown). Lower T-cell population numbers are achieved as a result. The number of control intervals used is 100 and the piecewise-constant profiles obtained are presented in Fig. 4. The total CPU time required for this optimization was 280.2 s.

The results depicted in Fig. 4 suggest that STIs are very effective in controlling disease progression in HIV-infected patients. Neither the drug-sensitive nor the drug-resistant virus strain grows in an uncontrolled manner and as a result the T-cell count is maintained above the threshold of AIDS for longer. During the early stages of optimised STIs, the schedule requires maximum ON (150 days) and minimum OFF (10 days) periods. This slows down the increase of the drug-sensitive strain, which is the main problem for a patient that has not developed any resistance. The optimized schedule is successful in reducing the total ON treatment to 74% of total therapy and the total side-effect index in this STI scenario is 880. In way of comparison, the S_e^T value obtained under current continuous treatments (600 mg RDV, 150 mg 3TC, 300 mg ZDV, twice daily) for the same treatment horizon was 3,640. This suggests that, on top of extending the life-expectancy of patients considerably, the optimized schedules presented here are able to reduce the impact of drug-associated side-effects markeably. In doing this, the patients also enjoy an increased number of drug-free periods. All these imply that the optimal strategies proposed here offer a considerable advantage to the patient.

B. Patient-specific treatment

So far, the optimal strategies proposed have been formulated for patients displaying the general characteristics of typical-progressors (the majority of patients in this category progress to AIDS after $\sim$10 years). No two individuals respond to infection and treatment in quite the same way, however, and this section investigates to what extent these strategies are able to extend the life-expectancy of other patients. Furthermore, this section presents a methodology for the formulation of patient-specific treatment planning.

The patient involved in this section is taken from the study by [40]. This patient falls in the category of typical-progressors (progression to AIDS after 5-15 years; [5], [26]), however, it is clear that progression to AIDS occurs considerably earlier for this individual (after $\sim$5 years; see Fig. 5) when compared to the majority of typical-progressors (progression after $\sim$10 years; see Fig. 2). The concentration-time profile for T-cells for this patient as predicted by the therapy model is presented in Fig. 5. In replicating the observed clinical data, only the immune system parameters (reduced proliferation of immune cells, $p_1, p_2, S_1, S_2, k_6, k_7$; action of CTLs and macrophages, k_3, k_5, k_{12}) have been altered (see Table IV); it is believed that this patient exhibited a weaker immune status [6], hence the faster progression to AIDS.

Treatment is initially administered according to the general STI schedule reported in Fig. 4. The results are not encouraging; the projected survival-time after initial infection for this patient is $2,800$ days (Fig. 6(a)), hence, the proposed schedule is not effective in extending the time before progression to AIDS occurs noticeably.

These results confirm that a general treatment framework is not effective and treatment has to be assessed on an individual basis. Optimal treatment planning for a specific patient involves: (a) monitoring the T-cell count of the individual down to $T = 350$ mm^{-3}, (b) prediction of HIV dynamics specific to that individual by fitting the model to data, and (c) formulation

TABLE IV
PARAMETER VALUES FOR AN UNTREATED PATIENT FROM THE STUDY BY [40]. THE REMAINDER OF THE PARAMETER VALUES ARE SIMILAR TO THE ONES FOR THE TYPICAL-PROGRESSOR'S CASE (TABLE I)

Parameter	Value	Units
p_1	0.19	d^{-1}
p_2	0.15	d^{-1}
S_1	55.6	mm^{-3}
S_2	188	mm^{-3}
k_3	4.16 x10^{-4}	mm^{-3}
k_5	2.78 x10^{-6}	mm^{-3}
k_6	3.01 x10^{-4}	mm^{-3}
k_7	5.5 x10^{-9}	mm^{-3}
k_{12}	3.7 x10^{-5}	mm^{-3}

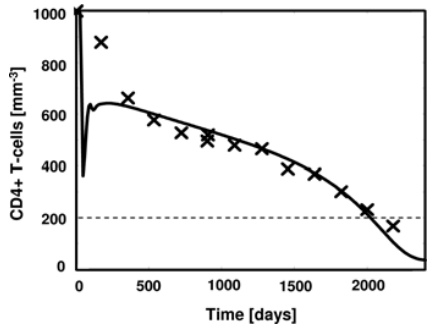

Fig. 5. Uninfected T-cell concentration-time profile over the course of HIV infection for an untreated patient from the study by [40] ($\times$). Results have been obtained by fitting the model to the data down to $T = 350$ mm^{-3}. Results show good agreement with the remaining data ($T < 350$ mm^{-3}). Dotted line marks progression to AIDS.

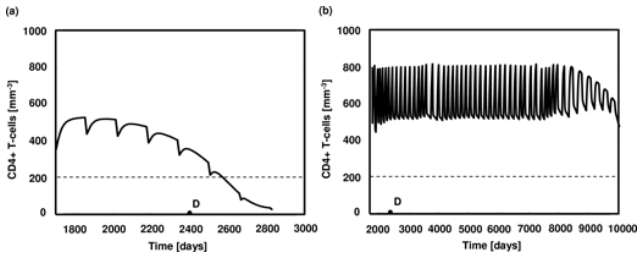

Fig. 6. Treatment studies on the patient [40] depicted in Fig. 5. Initiation of therapy is at $T < 350$ mm^{-3} ($\backsim 1,700$ days after initial infection). Application of (b) STI schedule reproduced from Fig. 4 for a typical-progressor and (b) patient-specific optimal treatment. Dotted line marks progression to AIDS. Point D indicates projected survival-time when no treatment is administered.

of the patient-specific treatment strategy initiated at $T < 350$ mm^{-3}. In the case of the patient in this section, the model predictions in Fig. 5 have been obtained by fitting the model to the data down to $T = 350$ mm^{-3}, and the predictions show good agreement with the remaining data in Fig. 5 (for $T < 350$ mm^{-3}). The patient-specific optimal treatment was then formulated and when administered was able to prolong the progression to AIDS to more than $10,000$ days (Fig. 6(b)), thereby emphasising the importance of formulating treatment schedules on an individual basis.

The results presented in this study are based on the predictions of mathematical models. Such models offer a simplified description of reality, as do virtually all modeling attempts. The present work has only dealt with the infection of CD4+T-cells and macrophages. Other cells (*e.g.*, dendritic cells) may become infected and may exhibit different kinetics. Also, direct cell-to-cell transmission of virus has not been considered and death of cells due to effects other than direct viral killing and natural death has been ignored. Furthermore, time delays should also be considered, hence, treating interactions between cells, virus, and drugs as non-instantaneous [8]. As far as the immune response is concerned, the effect of the suppressor cells has been assumed to be minimal compared to that of the CTLs. Furthermore, we have no control over the fitness of the drug-resistant strain [22]. In fact, mutations at every fitness level are likely to occur and the optimal treatment would be different in that case. Lastly, the drug-resistant virus has been modelled as one that has developed resistance to all drugs in an attempt to formulate optimal treatment strategies for this group of patients. This constitutes a large percentage of HIV-infected patients [41], nevertheless, inclusion of variables describing different drug-resistant strains is likely to result in a model which describes reality more closely. Another assumption in the model is lack of terms describing ageing factors. The age/ageing of individuals has been suggested [28] to be an important factor determining disease progression and response to treatment. In this work, the schedules run over long periods of time and the parameters are likely to change as the individual involved ages. As a result, the treatment might not necessarily be completely effective for the entire treatment horizon and a model accounting for this is likely to result in further improved predictions. We acknowledge these concerns and investigation of the results presented in this work through clinical or experimental studies is highly desirable.

IV. Conclusion

In this study an optimal control approach was considered in an attempt to formulate HIV treatment strategies. The optimization results suggest that a general treatment protocol cannot be proposed and treatment planning has to be produced on a case-by-case basis. Drug-specific treatment involves consideration of a side-effect index by using a well-documented side-effect chart whereas patient-specific treatment involves firstly the estimation of the patient-specific model parameters using clinical data, and subsequently the formulation of the treatment. The results presented in this work identified considerable scope for the improvement of current treatments, extending survival-time considerably and reducing the index associated with the side-effects of drugs markeably. The results suggest that STI therapy offers a promising alternative to current guidelines and should encourage further experimental and clinical work for validation purposes.

Appendix A
Pharmacokinetic model

Drug efficacies are given as a function of the concentration and effectiveness of the drug. For the drug regime involved (one PI: RDV, two RTIs: 3TC, ZDV), the RTI and PI efficacies are given by [42]:

$$u_1(t) = \frac{(C_2(t)/IC_{50}^2) + (C_3(t)/IC_{50}^3)}{1 + (C_2(t)/IC_{50}^2) + (C_3(t)/IC_{50}^3)} \quad (13)$$

$$u_2(t) = \frac{C_1(t)}{C_1(t) + \omega\, IC_{50}^1} \quad (14)$$

where $u_1(t)$ and $u_2(t)$ range from 0 to 1 and indicate RTI and PI efficacy, respectively, and $C_i(t)$ and IC_{50}^i indicate plasma and median inhibitory drug concentrations, respectively.

(14) presents a pharmacokinetic model describing drug concentration in the peripheral blood as a function of drug dosage. For simplicity, concentrations are modelled using a one-compartment open model with first-order absorption and elimination [42] and fixed pharmacokinetic parameters. Let $C_i(t)$ be the plasma concentration of drug i at time t. The

model between dosages, (*i.e.*, $t_l < t < t_{l+1}$) can be written as follows [42]:

$$C_i(t) = C_i(t_l)\, e^{-k_e^i(t-t_l)} + \frac{F_i D_i}{V_c^i}\frac{k_a^i}{k_a^i + k_e^i}[e^{-k_e^i(t-t_l)} - e^{-k_a^i(t-t_l)}] \quad i \in N,\ l \in n \tag{15}$$

where i is the index that denotes drugs; t_l is the time at which dose D_i is administered; F_i is the absolute bioavailability of drug i (the fraction of dose available); k_a^i is the absorption rate of drug i; $k_e^i = \frac{Cl_i}{V_c^i}$ is the elimination rate constant of drug i; Cl_i is the clearance of drug i; V_c^i is the volume of distribution of drug i; $C_i(t_0) = 0$; and Cl_i, V_c^i, $k_a^i > 0$.

The model in (15) is solved in *Mathematica 5.1*^{TM} for the drug regime consisting of RDV, 3TC, and ZDV and the results are plotted alongside respective clinical data with considerable agreement (Fig. 7(i)). The pharmacokinetic parameters used in the model are consistent with the manufacturers' recommendations ([44], [45]) and are given in Table V. For illustrative purposes, the time-course of concentrations of these drugs (all administered twice daily at standard dosage according to antiretroviral guidelines) over the first 3 days of dosing is plotted in Fig. 7(ii).

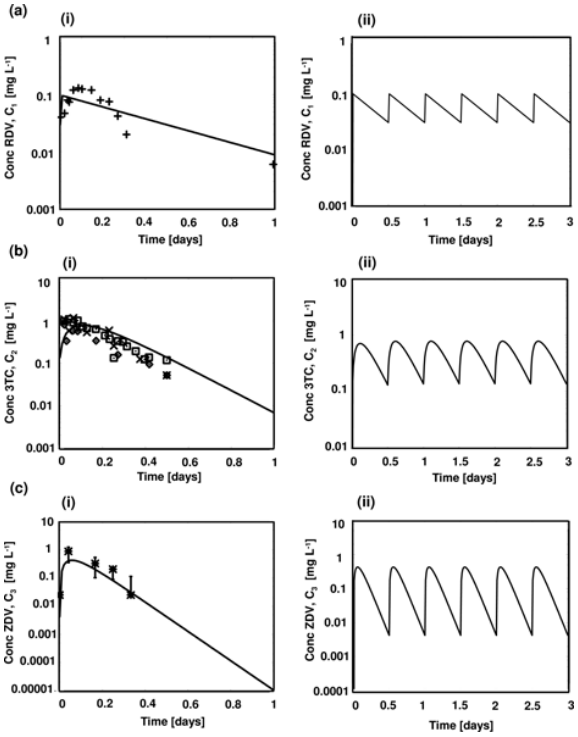

Fig. 7. (i) Model predictions for the concentration of three drugs (a-c) during treatment at standard dosage and steady-state conditions. Comparison with clinical data from: [46] (∗),[47] (+), and [48] (×,◇, □). (ii) Time-course of plasma concentrations of (a) RDV, (b) 3TC, and (c) ZDV at standard dosage over the first 3 days of dosing.

APPENDIX B
SIDE-EFFECT INDEX FORMULATION

The side-effect of a drug regime at a given time is given as a function of the concentrations of the drugs involved, the relative magnitude of the side-effect, and its observed frequency within a population. This has been presented previously in a review study [32] and is given in (16):

$$S_e(t) = \sum_{i=1}^{N} \bar{e_i}\, \frac{C_i(t)}{\overline{C_i}} \tag{16}$$

$$\bar{e_i} = \frac{e_i}{\max_{i \in N}(e_i)} \qquad i \in N \tag{17}$$

$$e_i = \sum_{j \in J_i} (q_j \cdot h_{i,\,j}) \qquad i \in N \tag{18}$$

In this system of equations, the side-effect index, $S_e(t)$, represents the magnitude of the side-effect of a drug regime at time t. J_i is the set of side-effects related to drug i, $C_i(t)$ is the concentration of drug i at time t, $\overline{C_i}$ is the mean concentration of drug i at steady-state at standard dosage (*i.e.*, according to antiretroviral guidelines), $e_i(\bar{e_i})$ is the magnitude (normalised magnitude) of the side-effect caused by drug i at standard dosage, $h_{i,j}$ is the frequency of individuals that present side-effect j when subject to drug i at standard dosage, and q_j is the relative magnitude of side-effect j, *i.e.*, "undesirability". This model is based on the additivity of the observed frequencies and magnitudes of side-effects, and considers that the magnitude of the side-effect index is proportional to the amount of drug administered. When solving the system of equations (16)-(17) above, the relative magnitudes of side-effects are modelled as 0.1, 0.2, and 0.7 for "weakly undesirable", "undesirable", and "strongly undesirable", respectively. Although fuzzy logic techniques [43] may be used to describe the transition from one state to another (*e.g.*, "undesirable" to "strongly undesirable"), this basic "metric" approach is considered here in order to reduce complexity. Furthermore, the observed frequencies of side-effects are modelled using values of 0, 0.05, 0.15, and 0.6 to represent the case where "side-effect has not been reported in individuals", "side-effect reported in less than 5% of individuals", "side-effect reported from 5% up to 15% of individuals", and "side-effect reported in more than 15% of individuals", respectively.

TABLE V
PARAMETER VALUES USED IN THE PHARMACOKINETIC MODEL. VALUES TAKEN FROM THE PRODUCT INFORMATION OF THE MANUFACTURERS ([44], [45]). PARAMETER τ REPRESENTS THE DOSING INTERVAL OF THE PROPOSED DRUG REGIME.

Parameter	RDV, C_1	3TC, C_2	ZDV, C_3
D [mg]	600	150	300
k_a [d^{-1}]	2.4	12	12
Cl [L d^{-1}]	1.48x10^4	5.6x10^2	2.69x10^3
V_c[L]	28.7	91	112
F	1.0	0.86	0.64
τ [d]	1/2	1/2	1/2
IC_{50} [mg L^{-1}]	0.11	0.34	0.13

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