Minireview

HIV models for treatment interruption: Adaptation and comparison

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Abstract

In recent years, Antiretroviral Therapy (ART) has become commonplace for treating HIV infections, although a cure remains elusive, given reservoirs of replicating latently-infected cells, which are resistant to normal treatment regimes. Treatment interruptions, whether *ad hoc* or structured, are known to cause a rapid increase in viral production to detectable levels, but numerous clinical trials remain inconclusive on the dangers inherent in this resurgence. In consequence, interest in examining interruption strategies has recently been rekindled. This overview considers modelling approaches, which have been used to explore the issue of treatment interruption. We highlight their purpose and the formalisms employed and examine ways in which clinical data have been used. Implementation of selected models is demonstrated, illustrative examples provided and model performance compared for these cases. Possible extensions to bottom-up modelling techniques for treatment interruptions are briefly discussed.

Keywords: Dynamic models; HIV; Cellular automata; Antiretroviral treatment

1 Introduction

Since its discovery in the early 1980s, as a principal factor in contraction of AIDS (Acquired Immune Deficiency Syndrome), the Human Immunodeficiency Virus (HIV) has been extensively researched [1,2]. As part of this effort, drugs which inhibit viral replication effectively, through interference with the viral replication cycle, have been shown to be immensely valuable.

State of the art treatment regimes, termed Antiretroviral Therapy (ART) consist of a combination of different drug classes; in most cases at least three are used [3]. The most common drug classes are Reverse Transcriptase Inhibitors (RTIs), more specifically Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs). Such substances aim to inhibit the enzyme Reverse Transcriptase, which plays a major role during cellular infection. Protease Inhibitors (PIs) are also common in ART and are targeted at the virus maturation step, which results in non-infectious virus production. Additionally, the recently-introduced drug class of Integrase Inhibitors (INSTIs) aims to reduce uptake of virus into healthy cells. Currently, health authority recommendations for combination therapy include two NRTI active agents and a third drug from either NNRTI, PI or INSTI [3]. These therapies are termed Highly Active Antiretroviral Therapy (HAART). The effect of the drug combination is the ability to maintain viral load levels in the blood below critical limits, which effectively reduces virus multiplication, fatal damage to the immune system and eventual progression to AIDS. The necessity of lifelong adherence to a strict treatment regimen, with toxic side-effects, has motivated investigations on feasibility of allowing patients to interrupt their treatment in a structured manner. With neither curative medication for infection nor an effective vaccine yet within reach, however, risk assessment is required [2]. The main barrier to the former breakthrough is the establishment of a so-called latent reservoir during early infection, (see [4] and references therein). This reservoir can stimulate an increase in viral load (to detectable levels) within days after treatment interruption; an effect known as *viral rebound*. The exact composition and location of the reservoir is still not completely known, and quantification is difficult [5]. Resting blood cells are thought to contribute and there is also evidence that viral replication is ongoing in parts of the body not directly targeted by the drug(s) [6]. Emergence of drug resistant strains [7], may also contribute to difficulties in managing treatment interruptions. A recent study has suggested also that short term pharmacological effects of multi-drug regimens may build drug resistance during treatment interruptions [8]. Currently, new drug classes, aimed at reactivating resting cells, are under investigation [9] but have yet to provide a comprehensive solution.

1.1 Treatment interruptions

Until relatively recently, patients were required to adhere lifelong to daily dosages of their medication in order to maintain viral suppression. In practice this requirement is not easy to fulfil, given the considerable cost and side effects of the drugs. The problem is especially acute in ~~resource- limited~~ resource-limited settings. Avoidance of side-effects [10], fear of stigma [11], or obstructed access to therapy due to political instability [12], are among the reasons for *ad hoc* treatment interruptions, which cannot be completely resolved. These *unstructured treatment interruptions* remain common.

Potential benefits (in terms of patient tolerance and resource optimisation), of specific treatment interruption schemes, have also been investigated. Such schemes, termed *structured treatment interruptions* (STI), have followed either fixed cycles, (e.g. week on/week off), or have been guided by concentration thresholds of specific markers, such as CD4+ T-Lymphocytes,[1] in the blood, (see [13] and references therein). Motivations for this research focus include cost-effectiveness of therapy administration and reduction of side effects. Earlier studies also investigated the hypothesis that treatment interruptions act as a stimulant to the immune system, eventually enabling it to control the virus without further treatment [14]. Additionally, it was hoped that drug-resistant viral mutations might be dominated by wild type virus following interruption, thus improving chances for successful treatment. The largest STI-related clinical trial to date (SMART) [15], used a (CD4+)-guided[2] approach to trigger treatment, although an increase in fatalities in the patient group with treatment interruptions, led to premature study termination. However, the percentage of cases with pre-existing immune system impairment (at severe stage) was high among the participants in this study, which may have contributed to the outcome [16]. Other STI studies either confirmed an increase in adverse events, or remained inconclusive [13]. No evidence for the stimulating effect of STIs on the immune system could be shown.

Nonetheless, the topic of treatment interruption is still actively under discussion since causes for treatment failure, following interruption, remain poorly understood, although missed drug doses result in decreased drug concentration and consequent effectiveness. In addition, loss of viral control and/or increase in drug resistant mutations may contribute [17]. Given that a clinical predictor for treatment failure has not been found, mathematical modelling has a role in using and augmenting existing clinical data to explore alternative solutions.

1.2 Modelling HIV: differential equations (top-down)

HIV attracted the attention of the modelling community shortly after the virus was discovered. Dynamic modelling was first applied at population scale [18], and, subsequently, to viral dynamics within the host [19]. Traditionally, dynamic models have relied on systems of nonlinear ordinary differential equations (ODE), which have their origin in predator–prey modelling. Such models have proved helpful in the HIV context, e.g. in the discovery that turnover rates of HIV and infected cells were much higher than anticipated [20]. Extensions and modifications of these models have also been applied to many other aspects of HIV infection, including treatment. A set of ODE representing a basic model is given by

$$\dot{T} = \lambda - dT - (1-\eta)\beta TV \tag{1a}$$
$$\dot{T}^* = \beta(1-\eta)TV - \delta T^* \tag{1b}$$
$$\dot{V} = kT^* - cV. \tag{1c}$$

The system consists of three separate ‘units’ or entities, (often designated in epidemiological studies as a ‘compartmental model’), while in our example, the ‘units’ are the three cell types, where variable T denotes uninfected/susceptible cells, T^* infected cells and V free virus particles. Parameter λ is the replenishment rate of healthy cells from the Thymus, and β is the infection rate. Parameters d, δ and c are death rates for healthy cells, infected cells and virus, respectively, and are not directly related to infection events. The model assumes a virus formation rate k, however, which is proportional to the number of infected cells. Thus, viral production rate is of *second order*, being dependent both on virus and uninfected cell numbers. This basic model also includes a term, which accounts for antiretroviral treatment. Parameter η represents treatment effectiveness, which reflects reduction in the overall infection rate.

While this model is simple enough to be used for mathematical analysis, clinical assays are available also to directly observe compartment behaviour, with estimates for formation and death rates available in the literature. Thus, the model can be used to estimate crucial parameters, such as infection rate and drug effectiveness through the inverse problem [21].

However, given the complex mechanisms, which have been identified for HIV infection, this model is, at best, a crude approximation. Biological features must be added through additional components and parameters, while preserving the basic model core. A model with higher degree of realism, for example, is given in [22] to be

$$\dot{T} = \lambda - dT - (1-\eta)\beta TV \tag{2a}$$
$$\dot{T}_L = \alpha_L(1-\eta)\beta TV + \left(\rho - a - d_L\right)T_L \tag{2b}$$
$$\dot{T}^* = \left(1-\alpha_L\right)(1-\eta)\beta TV + \delta T^* + aT_L - mET^* \tag{2c}$$
$$\dot{V} = kT^* - cV \tag{2d}$$
$$\dot{E} = \lambda_E + b_E\frac{T^*}{K_B + T^*}E - d_E\frac{T^*}{K_D + T^*} - \mu E \tag{2e}$$

where, in addition to the system in (1), Eqs. (2) include latently-infected cells T_L and immune response captured by the 'effector cells'[3] compartment E. Additional parameters include the fraction of cells α_L entering the reservoir upon infection, and those exiting the reservoir and becoming actively infectious, with rate a. Inside the reservoir, cells proliferate and die according to rates (ρ, d_L). Effector cells reduce the amount of infected cells through the first-order relation and rate m. Size of the effector cell compartment depends on a constant formation rate term λ_E and first-order death rate μ similar to the susceptible cell compartment. Moreover, effector cells are assumed to proliferate and die following Michaelis–Menten kinetics [23], where infected cells serve as 'substrate', with maximum rates of b_E and d_E and Michaelis–Menten constants of K_B and K_D respectively.

The ODE-approach assumes all model properties to be continuous variables. Thus, the system observed is envisaged as a 'well-mixed container', although this applies loosely at best for the human organism, which naturally consists of sections of different tissues and cavities, which are separated anatomically but connected through transport mechanisms, such as the blood and lymph stream and which are populated by discrete, cellular entities. In the case of HIV, infections occur predominantly in lymphatic tissues where the greatest proportion of susceptible lymphocytes resides. Intuitively, one would assume that the neighbourhood of virus-shedding infected cells is more susceptible to infection than that of remote cells. There is also evidence that HIV infection is more likely to occur through cell-to-cell contacts than uptake of free viral particles [24], which appears to support this view.

To analyse this spatial heterogeneity associated with HIV infections, additional dimensions may be introduced in models of Differential Equation type (by means of partial differentiation terms). The resulting systems of Partial Differential Equations (PDEs) are widely used to mathematically model biological tissues in oncology and for liver conditions, such as hepatitis [25]. For HIV, a system of coupled PDEs on a regular grid has been analysed [26], assuming viral diffusion and spatial dependence of healthy cell production given by

$$\dot{T} = \lambda(x) - dT - \beta TV \tag{3a}$$
$$\dot{T}^* = \beta TV - \delta T^* \tag{3b}$$
$$\dot{V} = NkT^* - cV + d\Delta V. \tag{3c}$$

In outline, the system described by Eqs. (3) is almost identical to that of Eq. (1). Additional here is the dependency of the recruitment rate of healthy cells on grid location, $\lambda(x)$ and a viral diffusion term with diffusion coefficient d and Laplacian Δ.

Moreover, the PDE approach is not limited to modelling spatial dependency. In [27], for example, the authors use a partial model derived from that of basic ODE form to reflect the age-dependent variation of infectiousness and burst rates of the infected cell compartment, thus permitting more in-depth analysis.

Simple ODE forms have been extended also, by inclusion of terms to reflect intracellular delay behaviour [28]. These Delay Differential Equation extensions (DDE), despite some advantages, are not widely used in the HIV context, however, possibly because they are less tractable to mathematical analysis.

Finally, it is worth noting that biological systems are inherently complex with very large number of variables and with parameter estimates difficult to obtain, (not least as these vary between subjects or are influenced by unknown factors). A not unreasonable assumption for simplification is that some model properties are stochastic. Stochastic Differential Equation systems, where ODE models are augmented by inclusion of probabilities ascribed to given events, have been considered, e.g. [29], where the authors analyse stochasticity in infection and inter-patient variation in early HIV onset.

In summary, ODE-type models can provide a good approximation to some aspects of HIV infection and have been widely used for biological systems, permitting explicit (in some cases) description of biological properties. Shortcomings, in terms of biological realism, may be compensated by versatility and improved tractability for mathematical analysis, together with availability of powerful numerical solution methods.

However, attempting to optimise biological realism, using DE model variants, can pose challenges. For example, despite the arguably higher degree of realism of the model defined by Eq. (2), its scope is more constrained than that of Eq. (1). This not least because components, such as latent reservoir size, are difficult to determine [5], so that obtaining reliable clinical data is typically non-trivial, as highlighted in Section 2. Together with the increased number of (patient-specific) parameters, this hampers application of the model for inverse problem approaches. Parameter values are thus assumed to be constant and are usually taken from published literature. Furthermore, the higher the complexity, the less tractable to direct mathematical analysis, so that, despite improved realism, the more sophisticated DE models are mainly used for theoretical studies, e.g. to assess the impact of variations of parameter values or the model structure, (see e.g. [30] for a recent review).

1.3 Modelling HIV: bottom-up

The top-down approach described above derives fundamental relations for a specific system, including further detail as more biological knowledge is incorporated. However, biological organisms consist of distinct entities operating over multiple scales, from genes and individual cells to organs, with emergent behaviour at fundamental levels contributing to that of the overall system. A bottom-up modelling approach takes account of changes to these separate entities to infer outcomes overall. Therefore bottom-up approaches appear to be well-suited to model biological systems on the premise that the underlying mechanisms are known in sufficient detail. These concepts, however,

are less readily described in mathematical terms (as for models of DE type), but do obey simple rules.

An intermediate approach considers ODE models, described by continuous variables, where these are considered to be discrete entities with formation and deletion events controlled by stochastic rules. Similar mechanisms to that of ODE apply but rates are treated as probabilities. A popular algorithm [31], proposed to implement such stochastic simulations for chemical reactions, has been applied also to HIV [32]. Interestingly, results of the stochastic simulation approach those of ODE equivalents when the number of modelled entities is large, (mean field approximation), suggesting that the former may be particularly useful for initial or relatively low viral loads, as found for early (or potentially resurgent) HIV infection, which is of interest here.

The Cellular Automata (CA) formalism was originally conceptualised as a way of representing and computing change in the human nervous system [33]. Models do not rely on a global system of differential equations but on a set of local rules applied to sites on a regular grid (or lattice), in which each individual site is updated, depending on neighbouring site status. The behaviour of such models is similar to processes in real biological systems where cells act as separate, independent entities, but are influenced by signals coming from their neighbourhood. Since cells are usually considered to be fixed relative to each other, these models provide a means to explore effects of spatial heterogeneity of infection within solid tissues, where viral particles are more likely to interact with neighbouring cells. This model form therefore relies on similar assumptions to those for PDEs, while assuming a bottom-up view by observing each entity independently, where these act without supervisory control, unlike the top-down case.

CA models have been used also to model certain aspects of the immune system [34] and have been extended to HIV [35]. With some refinements, it has proved possible to reproduce the time course of HIV infection [36], to expand this subsequently to include treatment [37], the latent viral reservoir [38] and different classes of drugs [39,40]. One widely-cited example for HIV has been the model of Zorzenon dos Santos et al. [36], which can be used to reproduce the three phases of HIV infection with a simple set of rules. This is covered in greater detail in Section 3.

More elaborate bottom-up approaches include Agent Based Models (ABM), which explicitly examine individual entities with specific properties and enable more complex rules representing an extension of the CA formalism. Agents are able to act independently and roam the model space, giving a more realistic representation of a biological system from the biologist's point of view. Several versions have been applied to HIV, (see [41] and references therein).

Using bottom-up models, the time-course of basic entities, (such as susceptible and infected cells [36], and immune system properties [42], amongst others), can be followed—as with ODE models. Furthermore, the emergence of these properties can be observed directly, enabling analyses of specific entity contributions, which are not accessible in formula-based ODE-type models. However, a detailed knowledge of the processes underlying the model assumptions is necessary, which is often more difficult to obtain than the broad-based view for top-down modelling.

In consequence, bottom-up models typically rely on numerical methods for solution, where these are frequently computationally demanding, requiring e.g. parallelisation and related techniques, such as grid computing [43]. However, given our growing knowledge of biological mechanisms involved in HIV-infection and advances in computing technology, we believe that these model forms deserve further consideration. Therefore, the primary focus here is the use of these alternative models for HIV treatment interruption to date, together with suggestions on how selected bottom-up models may be plausibly extended. We take a broad view on ways in which these models can be used to explore implications for interrupted HIV treatment.

2 Treatment interruption modelling

A review of purely DE-based models, while attractive from the point of view of coherence and comparison, neglects other less common approaches and their achievements. A contextual overview of top-down and bottom-up approaches has not, to our knowledge, previously been attempted for HIV treatment modelling.

Given the common criticisms, levelled at representation of biomedical systems, special attention is paid to the degree of biological realism built into the model structures for individual studies, (in so far as this is made explicit). The basis for parameter estimation and the use made of clinical data are examined also, with a view to highlighting these key study aspects, in order to suggest directions for (and constraints on) future research.

2.1 Model properties

The systematic approach, used for model assessment, based on predefined criteria, (see Table 1), includes general model properties, representation of key biological and physiological features, and use of clinical data within the study.

Table 1 Biological features implemented against model formalism.

Formalism	Total number of models	Models including biological features

		Immune response	Resistance	Pharmacology	Latent reservoir	Spatial aspects
ODE	35	14	20	12	13	0
ABM	5	5	0	0	5	5
Exponential	1	0	0	0	0	0
SDE	1	0	1	0	0	0
Stoch. Sim.	2	0	2	1	2	0

In total, 44 separate modelling studies were identified, (see Table 1). The degree of biological realism varied greatly across models examined. Earlier studies of treatment interruptions were published over the time period from 2006 to 2010, with an almost equal number appearing in the last 5 years, indicating that the topic is still actively discussed in the modelling community. Commonly-implemented features were drug resistance, a latent reservoir compartment, immune response and pharmacology. In contrast, spatial aspects were much less frequently considered, which is not surprising given the 'well-mixed' assumption of ODE models.

With respect to model purpose, most analyses (25 studies) were mathematical and of ODE type, e.g. analysis of Filippov systems [44], or involved combining mathematical analysis with numerical solutions [45,46]. The common aim of the studies identified, was to obtain threshold settings of model properties. In the case of treatment interruptions, these typically include baseline viral load or interruption schedules, which keep viral rebound within certain limits. Model parameters were usually based on values obtained from previously published studies, where these were derived from basic model forms or estimated based on clinical findings (see e.g. [19]).

In addition, a number of publications (10 studies) deal with so-called optimal control approaches. Following principles of control theory, the models describe controlled system output, usually pertaining to viral load, or number of infected or healthy cells. Treatment acts as an external input. Various designs have been proposed, from that of continuous dosage [47], to discrete drug administration [48]. Once again, model parameters were based on the literature.

A novel optimal control approach, for observation of treatment interruptions, has been reported also by [49]. The Castiglione et al. C-IMMSIMM model is agent-based and includes a very detailed reproduction of major functions of the immune system. Different immune cell types, such as various T-cells and Macrophages are modelled as moveable agents, acting on a simulated section of a lymph node, (as spatial component). The authors demonstrated that their model could be used to calculate optimal schedules for model instances under specified conditions, with pre-tuned parameters termed 'virtual patients'.

This successful application of a model, following bottom-up formalisms for treatment interruptions, has motivated the experiments described in the following sections, in which potential for augmentation is also explored.

Before we go into further detail, we will briefly discuss the issue of availability of suitable clinical or experimental data.

2.2 Data limitations of Structured Treatment Interruption (STI) models

Data, collected during clinical studies for STI evaluation, e.g. [15], were found to be insufficient to provide precise time-course information on properties required for accurate modelling. In general, clinical study criteria focus on different outcomes of specific treatment regimes, (such as interruption schemes or similar).

A small ~~sub-group~~ sub-group (nine), of the modelling studies identified, used clinical data to estimate parameters of ODE models. We found that clinical datasets were sourced from studies, conducted over the timespan, 2000–2006. We identified six separate clinical datasets [14,50–54], common to the sub-group of nine studies. Frequently-used data included those from the AutoVac study [51], in which 12 patients were subjected to a series of treatment interruptions. Cases of model calibration, based on a different dataset to that used for calibration, were rare. Only one study was found [49], which sought to validate the applied model in a qualitative way, using previously published data [55].

The datasets (identified above) provide a limited view on disease progression and outcomes by current criteria, not least since assay techniques have evolved in terms of sensitivity, detectable cell types and virus subspecies. Moreover, typically only viral load has been measured over time, so that parameter estimation relates to basic model types. Nevertheless, these datasets offer the finest-grained trajectories of patient-specific data for interrupted treatment to date. More recent datasets with appropriate granularity have not been identified by this review.

This scarcity of experimental data may explain the relatively infrequent mention in the literature of more complex top-down model forms, due to the difficulty of obtaining reliable parameter estimates. Furthermore, treatment interruptions can follow quite varied patterns, or be subject to different rules if structured, which also affects model parameterisation.

2.3 Additional experiments

A series of experiments for selected examples of top-down and bottom-up approaches were implemented using descriptions from literature, or by means of code obtained from the author, (where accessible). For the top-down formalism we used the ODE model, reported [22], and given in Eq. (1) as a reference, since this provided a trade-off between biological realism and complexity. As examples for the bottom-up approach, we implemented several Cellular Automata models [37–39], based on the model proposed by Zorzenon dos Santos et al. [36], which successfully reproduced the three-phase dynamics of HIV. We chose these model types to emphasise localised spatial aspects of HIV infection, which contribute to the immune system interactions (as referred to in C-IMMSIMM [49]).

In the original Zorzenon dos Santos et al. model [36], HIV infected cells are represented by sites on a square lattice of otherwise healthy cells and can infect cells in their neighbourhood. Infected cells lose potential to infect and eventually die after a fixed number of time steps. Dead cells may regenerate to healthy cells or become infected, with given probability, upon regeneration. Over time, regular structures of infected cells form over the lattice. A mean field approximation of the cell states over time gives a qualitative representation of the time-course of HIV infection.

Its remarkable properties motivated Burkhead et al. [56], to conduct a thorough mathematical analysis of the Zorzenon dos Santos et al. model. Amongst other findings, they postulated simplified models for each of the HIV phases reproduced by the model. For the primary phase, they found that an approximate quadratic relation applied, while the second, (latent) phase was found to depend on the formation of 'chronic sources' of infected cells which act as drivers in spreading infection. The third phase, however, which denotes transition to onset of AIDS as healthy cell levels decline, was found to follow a radically different pattern. The authors state that, in this phase, each lattice site can be described as an independent Markov Chain, where state changes depend only on the last state of the chain (or site) and not on those of neighbouring cells, as for the previous two phases. Based on this formalism, the authors argue that antiretroviral therapy reduces the transition probabilities from healthy to infected states (for RTI drugs) and increases death rates for cells that have an infected state (for PI drugs). By analysing the *stochastic matrix* of the Markov chain, the effect of drug intervention could thus be quantified. The approach was recently analysed in more detail by Hawkins et al. [57]. However, no forms of *interrupted* treatment were considered in either case, nor were findings explicitly used to infer biological outcomes or make predictions.

More recently also, a set of PDEs have been inferred from the Zorzenon dos Santos et al. model [58], and used to simulate numerically the spatial distribution of infected cells inside a lymph tissue patch. Conclusions on points of stability were drawn. However, the authors ~~emphasize~~ emphasise both the complexity of the resulting model, (which also does not consider any treatment effects), and the difficulty in obtaining stable numerical solutions.

In general, therefore, treatment interruptions have received little attention in investigations of the Zorzenon dos Santos et al. model, with the notable exception [59], which builds on the Sloot et al. formulation [37], to optimise treatment regimes. Unfortunately, no detailed analysis of this model [37], in the context of treatment interruptions has been reported. In consequence, the models implemented here, while derived from the Zorzenon dos Santos et al. baseline, explicitly consider different ways of including treatment. These are described in the following sections and are then further adapted (for both top-down and bottom-up approaches) to support structured treatment interruptions. Parameter estimates were obtained from the literature.

3 Results and discussion

3.1 Results

In our experiments, the effect of a treatment interruption of 8 weeks on the system, otherwise under treatment, was modelled. Results were obtained as either a numerical solution of the ODE or as the mean field approximations for the CA model.

Fig. 1 (top section) shows how an ODE model, (Eq. (2)—type given by [22]) behaves when treatment effectiveness is temporarily lowered. A rapid increase in viral load and number of infected cells can be observed at the time of interruption, as well as a delayed cytotoxic response. However, after treatment re-initiation, the system assumes a state almost identical to pre-interruption.

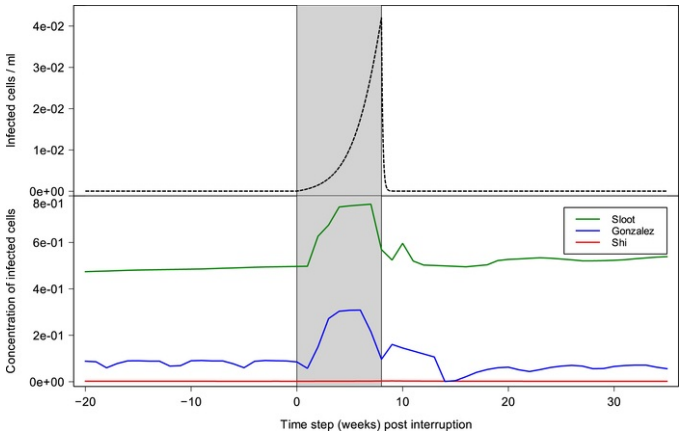

Fig. 1 Simulation of a treatment interruption (shaded grey) and subsequent re-initiation using an ODE model (top) and three bottom-up models using the CA-approach (bottom), baseline treatment effectiveness is set to 95%, average of 90 runs for CA models.

Results of a similar experimental setup using three different CA models are shown in Fig. 1 (bottom section). In the cases of two of the three CA models, simulated treatment caused a rapid increase of the viral number, (see also Fig. 1), which corresponds to the effect of viral rebound in terms of clinical observation. Due to the discrete nature of the CA approach, trajectories are less smooth than for the continuous ODE model. Remarkably, the Shi et al. model [38], shows no significant response despite being the only model explicitly including a latent reservoir. However, reservoir activation, as implemented in the model, appears to be slow compared to interruption duration. For the remaining models, viral rebound is marked and follows on rapidly from initial interruption, with viral load doubling (or concentration of infected cells increasing by one to several hundred percent), and proliferation of virus checked only on re-introduction of treatment.

The different implementations of treatment and effects of interruption for the different CA models are considered in more detail below.

3.1.1 Treatment modelling

Since CA models feature diverse response functions to treatment, trajectories of viral load behave differently for the same ‘effectiveness’ setting. For the Sloot et al. model [37], an exact response function could not be obtained, while assuming ‘constant effectiveness’ caused an increase in infected cell concentration, despite ‘highly effective’ treatment. However, model rules for treatment (reduction of susceptibility/infectiousness on a stochastic basis) were found to be similar to the Gonzalez et al. model. For reasons mentioned here, therefore, the Sloot et al. model was excluded from further analysis. Regarding the two remaining models, the respective authors approached implementation of treatment response differently.

In the Gonzalez et al. model [39], the response function takes the form of a distribution, controlled by baseline effectiveness and infected cell concentration at treatment initiation, i.e. its maximum. This *corrected effectiveness* controls the probability of a healthy cell’s entry to a protected state, (applicable to any healthy cell on the lattice). This ~~behavior~~ behaviour was found to interfere with a characteristic of the original Zorzenon dos Santos et al. model [36], namely the formation of regular, wave-like structures, which reflect the slow decline until non-recoverable depletion of healthy cells, as described in [56]. Since random healthy cells may become protected in the Gonzalez et al. model, these act as a kind of wave breaker because the remaining rules (e.g. for infected cells) remain unchanged. Fig. 2 (top) depicts the dissolution of regular structures after a few steps under simulated treatment, (showing ‘Markovian’ behaviour as suggested in [56]). Replication of infected cells is ongoing, despite a high level of suppression through treatment, which is not immediately evident from the mean field approximation, as in Fig. 1. This model does not include latently-infected dormant cells, which are also thought to contribute to the reservoir [4].

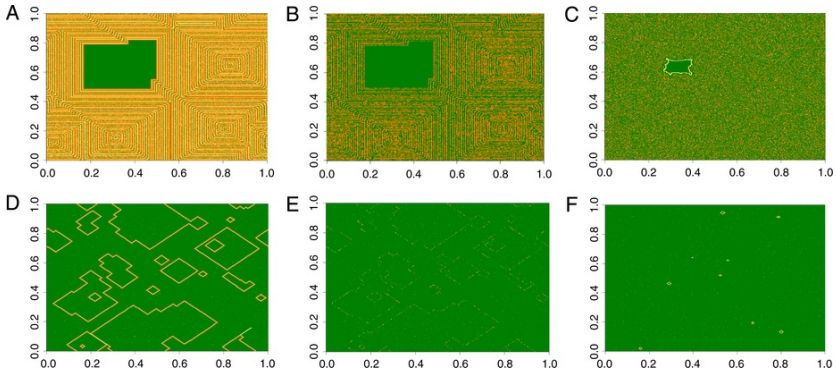

Fig. 2 2D lattice configuration of two CA models (A, B, C: Gonzalez et al.; D, E, F: Shi et al.) at different time points during simulated treatment and interruption: pre-treatment (A, D) at step 200, shortly after treatment initiation (B, E) at step 205 and shortly after interruption (C, F) at step 410. Green cells denote healthy states, while orange and yellow indicate infected states. Pre-treatment states show wave-like structures, dissolved during treatment. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The Shi et al. model [38], also features an additional state of latent infection, not present in the original Zorzenon dos Santos model. Latent cells have a long discrete latency period, after which they become actively infected. Treatment in the Shi et al. model is handled by way of reducing susceptibility of healthy cells, while avoiding a 'protected cell' state and also by taking into account spatial context of the cells. Here, an exponential response function effectively controls the size of neighbourhood around healthy cells, depending on treatment effectiveness and duration. Smaller neighbourhoods decrease the likelihood of infection since infected cells need to be close to healthy cells. Under treatment, disruption of the characteristic Zorzenon dos Santos et al. wave structures can also be observed as in the Gonzalez et al. model (Fig. 2, bottom).

3.1.2 Treatment interruption

Considering the impact of treatment interruption in the Gonzalez et al. model [39], lattice structure appears to preserve infected cell configurations prior to treatment initiation. Clusters of infected cells can continue to propagate during treatment. In consequence, control of further spread through protected cell states is lost upon treatment interruption and infected cells re-occupy this space, with rapid rebound of infected cell numbers. Fig. 3 shows different baseline levels of infected-cell concentrations due to different treatment initiation times. After simulated treatment initiation, viral levels stabilise at a certain level, which appears to depend on baseline viral levels. After simulated treatment interruption (causing an effect of viral rebound as shown in Fig. 1), and subsequent re-initiation with the same effectiveness as that in pre-interruption, viral levels stabilise again. Interestingly, these levels appear to be raised permanently due to the interruption.

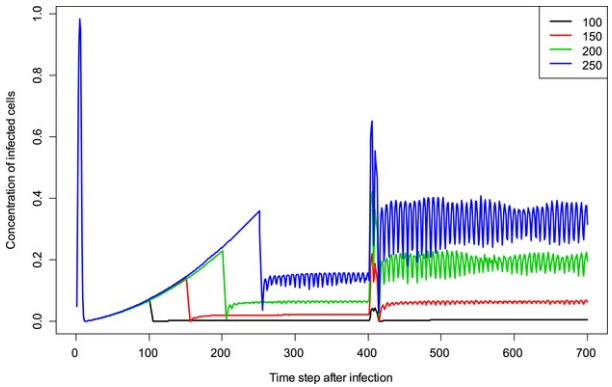

Fig. 3 Effect of the time of treatment initiation on infected cell concentrations. Treatment initiation was simulated from 100 to 250 time steps, each represented by a different plot. Treatment interruption occurred at step 400 for 8 time steps.

For the Shi et al. model, regular wave-like structures for healthy cell numbers reappear after interruption ends thus preserving model behaviour, (see Fig. 2). The inclusion of latently infected cells, which are not present in the other models, contributes to this behaviour. However, significant viral rebound does not occur (as seen, Fig. 1). This effect appears to be related to the parameter value for latency activation rate and the nature of the response function chosen by Shi et al. which reflects *slow re-establishment* of the virus, in contrast to the other models.

3.2 Discussion

3.2.1 Clinical data use and biological mechanisms

The evidence, from comprehensive search of the literature, is that clinical data are rarely used in these modelling efforts. Even where available, data for HIV treatment interruption are dated, scarce and insufficiently fine-grained for parameterisation of complex model forms. Typically, those datasets, which are widely cited, are more than a decade old and feature few measured biomarkers. No newer studies appear to have been conducted to provide more detailed measurements over the short time intervals suitable for rigorous calibration and validation of any dynamic model. Given the dearth of new data, it is possible that the truncation of the SMART study [15], has discouraged further efforts to investigate treatment interruptions in human subjects. In the past decade, however, assays for biomarkers have become more sensitive and some data on organs, other than blood, are now available [60].

3.2.2 Model forms

The almost exclusive reliance on top-down approaches, to model diverse aspects of HIV treatment interruptions and adherence, is marked. Since models are built from the same baseline (Eq. (1)) this is not surprising, and their application to viral infection problems is wide-ranging. Rough agreement with experimental data has been obtained, e.g. in investigation of viral and immunological properties of blood. However, all DE models make similar compromises and provide limited representation of the detailed immune system or become analytically non-tractable on inclusion of additional features.

Some important effects of HIV treatment, in particular, are rarely considered in such models. For example, clinical evidence suggests that HIV-infected cells mainly reside in lymph tissue [4] which resembles structure similar to solid tissue. Lowered drug concentrations, caused by poor penetration into these highly infected areas, have been found to be insufficient to suppress viral propagation completely [6]. This evidence suggests a highly heterogeneous distribution of HIV infection in different tissues, even of the same type, e.g. lymph. Therefore, localised effects should be taken into account in any model postulated, (see [61] and references therein).

Typically, simulations are employed for both these more complex systems of equations and for bottom-up approaches, where the latter have been applied more recently also to the problem of treatment interruption. In particular, the success of the C-IMMSIMM model for related questions in immunological modelling, suggests that bottom-up CA and agent-based approaches offer a viable alternative for modelling HIV treatment interruption. This notion is reinforced by the growing knowledge of biological mechanisms involved in HIV infection and advances in computing. Since C-IMMSIMM historically puts strong emphasis on faithful reproduction of major functions of the immune system, this suggests that a plausible strategy for model enrichment for treatment interruption, should involve different interruption intervals and duration, as well as e.g. pharmacological factors, subjected to rigorous sensitivity analysis.

Partial Differential Equations, which are commonly used to describe spatial heterogeneity, e.g. of a patch of lymph tissue, have rarely been applied in the HIV context. Analytical challenges for more complex PDE-systems, as pointed out in [58], possibly contribute to this limited use. However, inference based on simplified PDEs can provide theoretical underpinning, where only numerical solutions are otherwise available, (as in bottom-up modelling).

Conversely, rigorous mathematical analysis of bottom-up models, as described in Burkhead et al. [56], may provide improved descriptions of distinct model features and could be used to infer additional system properties.

3.2.3 Experiments with CA models

Recent clinical evidence, (as noted above), indicates that the distribution of infected cells, in different parts of the lymphatic system, may be highly heterogeneous. Rapid viral rebound to pre-treatment concentration appears to reflect impaired protection from treatment interruption and healthy cell depletion on the lymphatic tissue scale.

The Zorzenon dos Santos et al. model and its modifications [36–39], aim to describe localised effects on a matrix of lymphatic tissue. However, authors do not relate the matrix to specific organs (e.g. single lymph nodes) in detail; in consequence, these models appear to represent a generalised overview of lymphatic tissues inside an organism. Furthermore, no CA model, implemented here, has been designed explicitly to investigate treatment interruptions, so their capability for this extension must be critically considered.

The model of Shi et al. [38], offers some potential, since it defines a latently-infected cell state. However, the choice of an exponential treatment response function does not appear suitable for interruption study, since it assumes a fixed time period (e.g. 300 weeks) for treatment initiation, and does not take into account the possibility of repeated initiations. Some scope for possible alternatives does exist and includes specification of functions, which depend on, and respond to, variable properties such as e.g. cell counts.

For the ~~CA~~ Gonzalez et al. model [39], the configuration of infected cells, occupying the lattice, appears to play a major role in viral rebound. During treatment, ongoing replication and latently-infected cells are still present on the lattice, despite low viral loads. Upon interruption, these latently-infected cells rapidly ‘reclaim’ uninfected neighbours, resulting in significant rebound. Essentially, the behaviour of the model indicates that the *effectiveness* of the viral reservoir is influenced by its *spatial occupation* of the lattice, which offers interesting possibilities for further research. Furthermore, the interruption-induced increase of the areas containing infected cells on the lattice appears not to be reversed by subsequent treatment re-initiation. The aspect of infection leaving an ‘imprint’ on the infected tissue has, to our knowledge, not been considered before in HIV treatment modelling and appears to be a feature of lymph involvement. Interestingly, recent experimental results also suggest a strong

relationship between ongoing HIV infection and structural damage of lymphatic tissues, which can be delayed but not reversed through ART [62].

In addition, introduction of stochastic treatment effects into the deterministic Gonzalez et al. base model [36], causes overall behaviour changes, namely disruption of wave-like patterns to that of disparate or unordered spread of infected cells. This transition has been found to be irreversible in the experiments we have conducted, except for very low numbers of infected cells. According to the analysis by Burkhead et al. [56], lattice sites in clumped areas of infection, follow behaviour, which can be related to that of independent Markov chains, which corresponds to our findings. Their results also show that introduction of simulated treatment leads to a more aggressive disease progression due to the onset of 'mathematical chaos'. However, the behaviour described relates to homogeneous treatment and infection of the lattice, so that Markovian behaviour applies throughout. Heterogeneous infection (localised area or shape of 'chaotic' regions) was not considered, nor were (repeated) treatment interruptions taken into account. Incorporating these aspects into the Markovian argument could provide an interesting target for extension of the mathematical analysis. A possible direction could include assessment of the impact of the treatment interruption-induced change of size and shape of non-Markovian regions on the long term-behaviour of the system, obtained through the stochastic matrix. These shape and size effects may account for a correction to the estimates obtained under the assumption of homogenous infection and treatment.

Further, assessment of stochasticity in model rules, and how this affects outcomes, remains to be explored together with choice of alternative response functions to treatment, ideally to include pharmacological effects. Incorporation of stochastic features in this way implies use of parallelisation methods, not least for optimisation of the parameter space, together with additional sensitivity analyses. Nevertheless, given these and other highlighted potential refinements, CA models can offer further insight in understanding the effects of HIV treatment interruptions.

4 Conclusion

Through advancements in treatment regimes, HIV is now viewed as a chronic disease. However, treatment interruptions, (both unstructured and structured), are common and can seriously disrupt management of HIV infection, with potentially fatal outcome.

Our review of the literature has shown that mathematical (ODE) models of HIV treatment interruptions predominate and that clinical data are rarely used in modelling, owing to their scarcity and poor granularity. Extended DE models, such as PDEs have not been widely used to date and, while useful, present considerable challenge due to the mathematical treatment of perturbations in these systems, which require extensive numerical methods.

Given the limitations of top-down models in terms of detailed representation of the immune system, bottom-up approaches can provide a viable alternative and offer additional insight, (supported by experimental findings). While unified Agent Based approaches exist for immune system models, such as C-IMMSIMM or SIMMUNE [42], treatment interruptions have attracted limited attention in the modelling literature to date, but remain an important clinical concern. Of particular interest is the spatial heterogeneity in lymphatic tissues of both infected cells and antiretroviral drug, the distribution of which has been found to be critical in recent clinical studies. Our own experimental results indicate that there is an irreversible change in spatial structure of infection patterns in simulated lymph tissue due to interrupted treatment. This may account for the detrimental effect, of such interruptions, to the lymphatic tissues and the immune system which, while clinically observed, has yet to be clearly quantified. Mathematical analysis on the extended model, (possibly extending the approach of Burkhead et al. [56]) may prove useful in obtaining enhanced top-down representation in this context.

In summary, extending the simple rules of bottom-up models (like CA and ABM), in the context of HIV treatment interruptions, provides a different perspective to that of traditional top-down models. Additionally, it may suggest new directions for investigation of changes in lymphatic tissue structure from which top-down modelling quantification and analysis can benefit. Augmented CA model sensitivity analysis is clearly required, together with practical solutions, (efficient parallelisation and clustering), to meet computational demands. Nevertheless, it does seem that revisiting bottom-up approaches, (CA and AB models), may contribute further insight to successful management of HIV treatment interruptions.

Acknowledgement

The authors would like to acknowledge useful discussions with Ricardo Cruz regarding CA model implementations. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Footnotes

1CD4+ T-Lymphocytes act as indicators to impairment of the immune system due to HIV infection. Low levels of these in blood are associated with opportunistic disease and onset of AIDS.

2CD4+-guided STI schedules for treatment interruption and re-initiation, base decisions on the violation of predefined limits of patient CD4+ count in blood.

3'Effector cells' in the cellular immune system, after activation from a naïve state, cause a cytotoxic response to pathogen. CD8+ T-cells is the effector cell type, found to be most effective in the HIV context.

Highlights

- Treatment Interruption models almost entirely Differential Equation-based to date.
- Model calibration reliant on a small number of datasets, more than a decade old.
- Bottom-up methods can help enhance aspects of the problem.
- Cellular Automata models may give insights into e.g. latent reservoir persistence.
- Treatment interruptions though pose challenges to existing models of either type.

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