Physica A 483 (2017) 44–56

Contents lists available at ScienceDirect

Physica A

journal homepage: www.elsevier.com/locate/physa

Minireview

HIV models for treatment interruption: Adaptation and comparison

Andreas Hillmann *, Martin Crane, Heather J. Ruskin

Advanced Research Computing Centre for Complex Systems Modelling (ARC-SYM), School of Computing, Dublin City University, Dublin, Ireland

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.

ARTICLE INFO

Article history:
Received 10 June 2016
Received in revised form 28 January 2017
Available online 4 May 2017

Keywords:
Dynamic models
HIV
Cellular automata
Antiretroviral treatment

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.

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* Corresponding author.
E-mail address: andreas.hillmann2@mail.dcu.ie (A. Hillmann).

http://dx.doi.org/10.1016/j.physa.2017.05.005
0378-4371/

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 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,

[1] CD4+ 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.

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