values is normally quite satisfactory. Fuzzy logic and other rule-based schemes can handle this problem, but the schemes become more complex as larger numbers of inputs and outputs are involved. We have had success using penalty functions as soft constraints on the CO values, in a model predictive control formulation [15]. In a clinical environment it will be necessary to have a user-friendly interface with relatively few parameters that need to be specified or adjusted for satisfactory control. The first successful feedback control device for a surgical environment is likely to focus specifically on mean arterial pressure, with better integrated display and alarming functions for other variables, such as cardiac output.

There are a number of challenges that need to be overcome before widespread use of this technology in the operating theatre. One of the primary challenges is the development of a user-friendly interface with a limited number of "knobs" for controller tuning. Many parameters used in a multivariable MPC control law (constraints, weights, prediction horizons, etc.) and the model weighting estimator (primarily convergence factors) can be adjusted. Much of this information needs to be "distilled" to some simple "up–down" buttons to change the speed of response of the control strategy. It is important that the set-up procedure not be substantially more difficult or time-consuming than the current open-loop techniques.

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IV. Structured treatment interruptions: A control mathematical approach to protocol design

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1. HIV/AIDS therapy – a control engineering problem

Current research on HIV therapy is diverse and multidisciplinary. Engineers however, were late in joining the research movement and as such, engineering literature related to HIV chemotherapy is limited. HIV chemotherapy and control engineering have a lot in common [1–6]. From a control theoretic perspective, HIV chemotherapy can be seen as the control of a time varying nonlinear dynamical system with constrained controls. Once a suitable model has been developed or identified, control system theoretical concepts and design principles can be applied. The adopted control approach or strategy depends primarily on the control objectives, performance specifications and the control constraints.

Highly active antiretroviral therapy – HAART, generally entails the concomitant use of reverse transcriptase inhibitors – RTI and protease inhibitors – PI. Viral load suppression to below levels of detection with the use of HAART can be achieved within 3–4 months of initiating

therapy [7]. However, the drug dosage efficacy required to maintain this virus suppression is high. This introduces the HAART associated problem of instantaneous and cumulative toxicities.

In this paper, structured treatment interruption schedules are derived for when varying upper viral load limits are set on the virus rebound. The intention is to reduce drug exposure and consequently, the associated toxicity and cost of therapy. The appropriateness of imposing each viral load limit is assessed and the derived Off/On schedules will be compared with schedules that have been used in some STI clinical trials.

2. Structured treatment interruptions

Structured treatment interruptions – STI of HAART is being considered as an option to continuous therapy. Besides reducing drug exposure, STI can be used for autoimmunization or salvage therapy. Numerous clinical trials have been conducted in order to determine the immunological and virological benefits of STI for patients with HIV infection, as well as to determine the best protocol. STI for autoimmunization has been clinically proven to be more successful in patients who initiated therapy during the acute and very early chronic infection stages [8], than it is in patients who initiated therapy in the chronic infection stage [9,10]. However, the acute infection stage does not last for very long and most HIV infected persons are in the chronic infection stage. The problem with HAART interruption for the chronically infected patient is that the virus rebounds within days [11] with an associated decline in CD4+ T cell counts.

Deriving an STI protocol that will benefit most patients is still problematic. There is variability in response between individuals within a clinical trial, as well as between individuals in trials with similar protocols. The underlying cause for this variability in response is complex. In clinical trial conditions where poor adherence has been ruled out, this variability in response has been linked to inter-individual variations in drug uptake, as HIV drug pharmacodynamics, pharmacokinetics and adverse reactions are genetically predisposed [12,13]. One of the objectives of STI should be to improve the determination of immune competence in chronically infected patients, and to develop tests that may then predict which patients will be the best candidates for STI [14]. The general idea is that STI, just like therapeutic drug monitoring, is not for everybody. There is therefore, a need to focus on obtaining viral load time response estimates [15], as well as monitoring both the viral load and CD4+ T cell count so that therapy can be resumed before the virus rebound occurs.

The problem with STI protocol design is that most assays used in clinical practice have a detection cut-off limit of 50 copies per mL of plasma. This makes timing viral load rebounds and deriving a suitable STI schedule problematic because the virus dynamics under consideration occur at viral loads that are below the level of detection. The maximality of virus suppression below the detection cut-off is therefore unknown because there usually is no model that one can use as a guide. This is problematic because these unknown initial system conditions when therapy is interrupted or resumed, do influence its transient response.

3. The HIV/AIDS extended model

The model presented by Eqs. (1)–(6) was adopted for this study. This so-called extended model is single compartment and illustrates the virus and target cell dynamics in plasma. The model is useful because it can simulate persistent virus replication under potent HAART [16]. The model can also simulate differential drug penetration into different target cells co-circulating in plasma [17]

$$\dot{T} = s_T + pT(1 - T/T_m) - d_T T - \beta_T TV \tag{1}$$

$$\dot{T}_1 = (1 - \eta_{rt})q_1\beta_T TV - kT_1 - \delta_1 T_1 \tag{2}$$

$$\dot{T}_a = (1 - \eta_{rt})q_a\beta_T TV + kT_1 - \delta_a T_a \tag{3}$$

$$\dot{M} = s_M - d_M M - \beta_M MV \tag{4}$$

$$\dot{M}^* = (1 - \alpha_{rt}\eta_{rt})q_M\beta_M MV - \mu M^* \tag{5}$$

$$\dot{V} = (1 - \eta_{pi})r_T T_a + (1 - \alpha_{pi}\eta_{pi})r_M M^* - cV \tag{6}$$

The state variables T, T_1 and T_a are the plasma concentrations of the uninfected, latently infected and actively infected CD4+ T cells, respectively. M and M^* are the uninfected and infected macrophage cells, while V represents the infectious free virus particles. Parameters are presented in Table 2.

The immune response to the virus is not explicitly modelled. Instead the effects of the said immune response are incorporated into relevant model parameters. In particular, the rates at which CD8+ T cells kill infected cells and virus are incorporated into the death rate constants δ_1 and δ_a of the infected cells, and the clearance rate constant c of the virus. Parameters δ_1, δ_a and c therefore, "collectively reflect the immune system's *defensive* strength against HIV infection" [18]. Similarly, parameters β_T and r_T "collectively reflect HIV's *offensive* strength"[18] against the immune system.

The HIV/AIDS model (1)–(6) is identifiable [19,20], where identifiability is a basic system property of whether all parameters can be calculated from the measured output. Basically, the identifiability property of this system depends on the variables that are taken as the measured output. Table 1 summarizes the results for when various model variables are the measured outputs. The case for when the model is reduced and macrophage cells are not included is also presented.

This identifiability study illustrates how model based control analytical approaches can complement clinical studies. This also shows that the model based STI schedule design approach can be practically implemented, as the required measurements can be obtained from when one first initiates HAART.

Table 1
Minimum number of measurements required for a complete estimation of all the model parameters

Measured	T	T_1	T_a	M	M^*	V
T, V	15	1	1	1	1	17
T, M, V	11	0	0	11	0	13
T, T_a, V	5	1	6	1	1	10
T, V	6	1	1	–	–	8

Ref. [19] excluding proliferation.
– Macrophage cells not modelled.

4. STI protocol design

In most clinical trials, the participants had been on HAART long enough and had a record of sustained viral load suppression below 50 copies per mL of plasma. To achieve these pre-STI conditions for this paper, a model predictive control – MPC based optimal dosing sequence was previously derived using the parameters in Table 3 [22] with various input and output constraints put in place. Viral load suppression was attained and maintained and transient viral load rebounds, or 'blips' that are usually experienced by individuals on HAART, were eliminated. The viral load response is as illustrated in Fig. 1, where therapy was initiated 300 days from initial infection for 300 days. The resulting combined RTI and PI efficacy η_{co} that was required to maintain viral load suppression as well as the systems state at day 600 are presented at the bottom of Table 3.

The strategy then, now that virus suppression has been attained and maintained, was first to determine the conditions for interrupting and resuming therapy. The next step was then to derive STI schedule options that work for the chronically infected individual with the parameter set in Table 2.

For each schedule option, the following will be evaluated or considered:

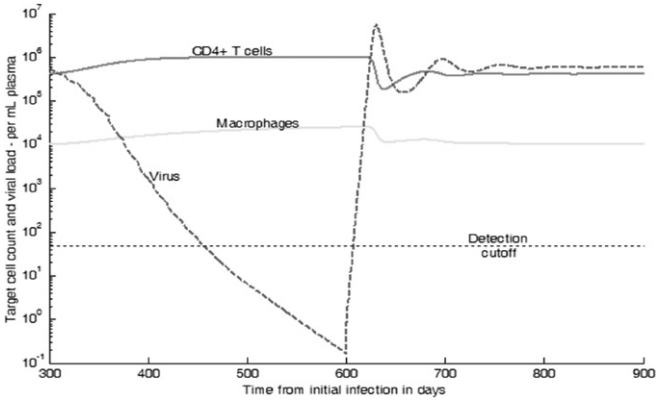

Fig. 1. Viral load suppression with HAART and rebound to pre-HAART values when therapy is discontinued. Therapy was initiated at day 300 and was terminated at day 600.

- Percentage reduction in total drug exposure when compared to continuous HAART.
- The ease of implementation, or lack thereof.
- Ways of improving the appeal of the schedule.

4.1. Off/On HAART – getting the timing right

The viral load in most cases rebounds and target cell counts decline to pre-HAART levels when therapy is not re-initiated after an interruption, as illustrated in Fig. 1. Therapy therefore, has to be re-initiated before the viral load rebounds to a value that is above the prescribed upper limit. This upper limit has varied from 50 copies per mL plasma, to 200 copies per mL plasma, and even 500 copies per mL plasma, depending on the trial and its objectives. The same will be done in this paper and the appropriateness of imposing each viral load limit will be assessed. The control sequence was as follows:

- Interrupt HAART until VL $\geqslant$ upper cut-off [50, 200 or 500 copies per mL plasma] or CD4 $\leqslant T$
- Resume and maintain HAART until VL $\leqslant V_{STI}$
- Repeat Off/On cycle for 300 days

where T is the pre-treatment T cell count, while V_{STI} is the viral load when STI is initiated. Therapy is considered to have failed if the viral load cannot be kept below the cut-off limit.

STI schedules were derived for a variety of viral load – VL upper limits (VL < 50, VL < 200 and VL < 500 copies per mL plasma). Fig. 2 shows the viral load response when various upper viral load limits are imposed. The corresponding Off/On periods and percentage reduction in drug exposure were then calculated and results are summarized in Table 3.

Results show that imposing lower viral load limits resulted in shorter Off/On cycles. It can also be seen that these short Off/On cycle schedules have a relatively higher percentage reduction in total drug intake. As it appears, increasing the viral load cut-off limit is a case of increased risk of drug resistance with no reward.

From a total drug intake perspective, the 7/21 days cycle schedule that resulted when VL < 50 limit was imposed, was the best as it results in the highest reduction in total drug intake of 25%. Another advantage of this schedule is that it can be easily implemented as it is convenient to use. Results are summarized in Table 3.

Overall, the two factors that determine the failure or success of the STI schedule appear to be:

- whether or not the OFF HAART period is short enough, given the upper viral load limit and initial pre-STI conditions, and
- whether or not the ON HAART period is long enough to re-establish the conditions (or similar) that existed before the interruption.

Table 2
Parameter estimates and measurements when STI is initiated

Parameter	Value	Parameter	Value	Parameter	Value
s_T	10^4 mL^{-1} day^{-1}	d_T	0.01 day^{-1}	β_T	4.5×10^{-8} mL day^{-1}
P	0.02 day^{-1}	T_m	10^6 mL^{-1}	q_1	0.005
q_a	0.55	δ_1	0.01 day^{-1}	δ_a	0.5 day^{-1}
K	0.025 day^{-1}	s_M	150 mL^{-1} day^{-1}	d_M	0.005 day^{-1}
β_M	1.75×10^{-8} mL day^{-1}	q_M	0.95	μ	0.05 day^{-1}
r_T	240 cell^{-1} day^{-1}	r_M	35 cell^{-1} day^{-1}	c	5 day^{-1}
η_{rt}	[0; 1)	η_{pi}	[0; 1)		
α_{rt}	0.85	α_{pi}	0.55		

Refs. [1,16,6,21].
Conditions when STI is initiated: V, 0.17 copies mL^{-1}; T, 1000 cells μL^{-1}; η_{co}, 0.82.

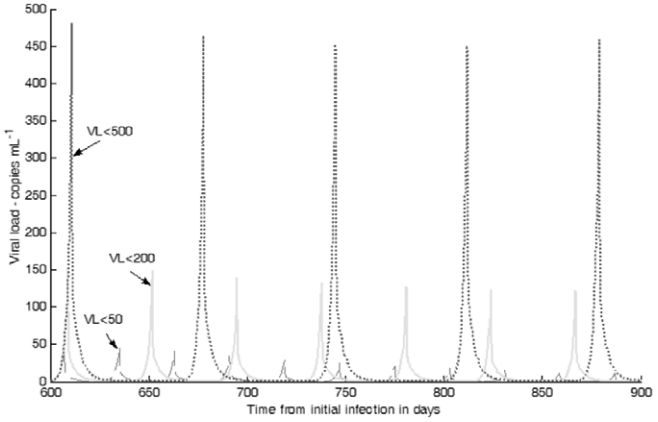

Fig. 2. Getting the timing right for varying viral load upper limits. Pre-STI conditions are presented in Table 2.

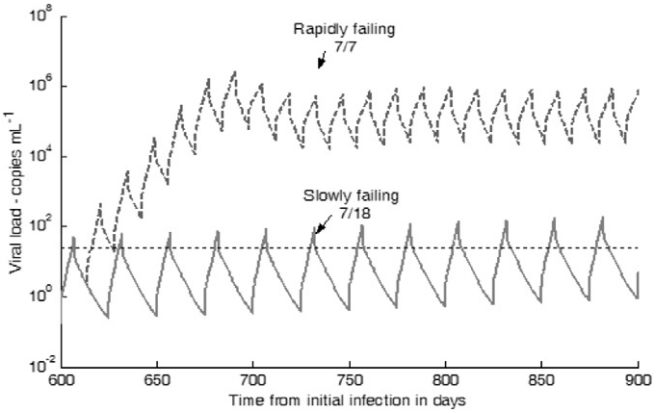

Fig. 3. Designed to fail: effect of failure to re-establish conducive conditions on successive viral load measurements.

Table 3
Getting the timing right with varying viral load upper cut-off limits

Viral load cut-off	Duration Off/On (% reduction)
$V < 50$ copies mL^{-1}	7/21 days (25)
$V < 200$ copies mL^{-1}	9/34 days (20.9)
$V < 500$ copies mL^{-1}	11/56 days (16.4)

The values indicate time off HAART, the time on HAART and the percentage reduction in total drug exposure.

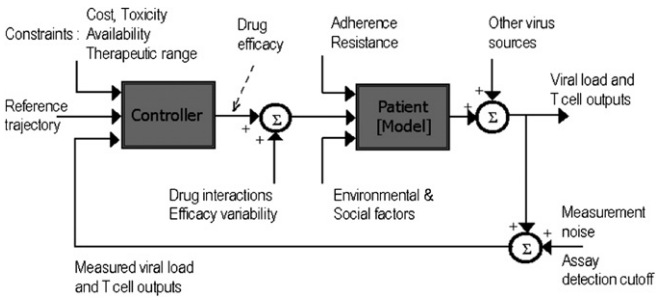

Fig. 4. HIV/AIDS control system block diagram.

When all the foregoing is assessed, this seems to suggest that in the absence of immune control of the viral load, as is usually the case in chronic infection, STI schedules with equal OFF/ON periods, such as the 7/7 days schedule used in the clinical trial by Ananworanich et al. [9], were designed to fail, as illustrated in Fig. 3. The reason for the high failure rate in this trial is because the virus is not adequately re-suppressed when therapy was resumed after an interruption.

The results in Table 3 suggests that, besides the 7/7 days trial, the individual considered in this paper would have also failed, in the following clinical trials:

- the 2 weeks/8 weeks trials by Oxenius et al. [10] and Fischer et al. [11] because the 2 weeks off therapy is too long and would allow the viral load to rebound to high levels.

Similarly, the said individual would have had a positive outcome in the following clinical trial:

- The 1 week/3 weeks trial by Lori et al. [23], though no conclusions about resistance can be drawn in this case.

5. Conclusions

The following conclusions can be drawn from this study: This paper has presented an STI design tool that can be used to evaluate clinical trials with. Overall, the two factors that determine the failure or success of an STI schedule are:

whether or not the OFF HAART period is short enough, given the upper viral load limit and initial pre-STI conditions, and whether or not the ON HAART period is long enough to re-establish the conditions (or similar) that existed before the interruption. Failure of most STI clinical trials can be attributed to failure to re-establish these pre-interruption conditions.

In the absence of an invoked immune control of the virus, STI schedules with equal Off/On periods, such as the 7/7 days and 30/30 days schedules, were designed to fail. Protocols with lower viral load cut-off limits result in shorter Off/On cycles. Also, these short cycle STI schedules have a relatively higher percentage reduction in total drug intake. As it appears, increasing the viral load cut-off limit increases the risk of drug resistance with no reward.

6. Research areas in HIV/AIDS modelling and control

Fig. 4 is a system diagram for HIV control. HIV therapy has many and often conflicting objectives as well as many constraints on the control inputs. Furthermore, as illustrated in Fig. 4, there are many points of disturbances and much uncertainty. Obtaining accurate measurements is problematic because of the viral load assays that are currently used.

Antiretroviral agents are toxic and now that the focus has shifted from virus eradication to managing a chronic infection, this presents an opportunity to derive optimal dosing strategies that strike a balance between aggressive therapy and toxicity reduction. Furthermore, the optimal time to initiate therapy during the course of HIV infection still remains unclear [5,7]. In fact, most areas identified in the HIV/AIDS control system diagram above, provide opportunity for further research.

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V. Modeling and control of the anticoagulant drug heparin

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1. Overview

The scope of the medical problems which require the use of anticoagulant drugs cannot be overstated. Arterial thrombosis is a major contributor to acute myocardial infarction, stroke, and renal causes of death in the United States. Venous thromboembolism is the most common non-surgical cause of death in patients hospitalized for major orthopedic procedures, a frequent non-obstetrical