Development of Structured Treatment Interruption Strategies for HIV Infection

Eric S. Rosenberg, Marie Davidian, H.Thomas Banks

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Eric S. Rosenberg[a,c*], Marie Davidian[b,c], H. Thomas Banks[c]

[a]*Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA*
[b]*Department of Statistics, North Carolina State University, Raleigh, NC 27695-8203, USA*
[c]*Center for Research in Scientific Computation, North Carolina State University, Raleigh NC 27695-8205, USA*

Abstract

Human immunodeficiency virus Type-1 (HIV) progressively destroys the body's ability to fight infection and neoplasm by killing or damaging cells that are part of the body's immune system. Considerable progress has been made in the treatment of HIV infection through the development of potent, highly active antiretroviral therapies, whose goals are to effect sustained suppression of measurable levels of virus in the body and to restore and preserve immunological function. However, continuous treatment with these powerful agents involves significant cost and patient burden and can lead to toxicities, development of drug-resistant virus, and problems with adherence. Thus, there is great interest in treatment strategies that can control HIV infection without the need for continuous, lifelong use of these drugs. These issues have led to consideration of treatment strategies known as structured or supervised treatment interruption (STI), which usually involve cycles of treatment withdrawal and re-initiation. We review the considerations underlying HIV therapy, describe the biological and clinical rationale for STI, discuss challenges involved in specifying STI strategies, and describe how design of STI strategies may be assisted by mathematical models of the within-patient dynamics of HIV.

1. Introduction

Since the advent and widespread use of potent antiretroviral therapy, there has been a profound decrease in morbidity and mortality from HIV and AIDS related illnesses (Detels et al., 1998; Murphy et al., 2001; Palella et al., 1998). Despite initial optimism surrounding the possibility of eradicating HIV with highly active therapy (Perelson et al., 1997), it is now evident that, due to the persistent nature of HIV and the establishment of latently infected reservoirs, it is unlikely that the virus can be eradicated from the body. Therefore current therapeutic strategies will need to be continued for life (Finzi et al., 1999; Siliciano et al., 2003). A lifelong commitment to anti-HIV therapy is often complicated by side-effects, toxicities (Martinez et al., 2001; Smith, 2002),

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[*] Corresponding author. Tel. +1 617 724-7519; fax +1 617 726-5957.
 E-mail address: erosenberg1@partners.org (E.S. Rosenberg)

adherence issues, problems with drug resistance (Ledergerber et al., 1999; Phillips et al., 2005; Richman et al., 2004), high cost of therapy, and life style issues. Once therapy is initiated, it is common for patients to change therapeutic regimens and, in fact, the median "life-span" of an initial regimen is only 1.6 years (Chen et al., 2003).

Given the inherent difficulties in committing to taking continual lifelong therapy, the concept of intermittent or cyclical therapy has been of significant scientific and clinical interest. This has led to consideration of treatment strategies referred to as "structured" or "supervised" treatment interruptions (STI), which involve having patients take antiretroviral therapy for some period of time, followed by treatment interruption and possible re-initiation, perhaps through several cycles of these steps.   However, although STI regimens have been proposed based on experience and expert opinion and have been studied clinically in both humans and animals (Lisziewicz et al., 1999; Lori et al., 2000; Lori and Lisziewicz, 2001; Rosenberg et al., 2000; Walker and Rosenberg, 2000; Wodarz et al., 2000), the potential benefits of STI are still not established.   This is likely due in part to the fact that previous studies of STI have been hampered by a lack of reliable information on how best to design interruption strategies.

The fact that the progression of HIV disease is governed by the interplay between the virus and the immune system offers a unique possibility for constructing STI strategies. Since the seminal work of Ho et al. (1996) demonstrated that the time course of HIV RNA viral load (the concentration of copies of viral RNA present in the body) can be described by mathematical models, there has been considerable interest in developing such models to describe hypothesized interactions between the virus and immune system taking place within a patient and in using them to provide possible explanations for the mechanisms responsible for the observed progression of HIV and for the effects of treatment (e.g., Adams et al., 2005; DiMascio et al.s, 2004; Dixit and Perelson, 2004; Pereleson et al., 1997). Thus, these so-called HIV dynamic models offer a potential foundation for designing and studying STI strategies.

In this article, we review current practices for the management and treatment of HIV, discuss the practical and scientific rationale for STI, and recount experience with STI in the clinical setting. We then provide an introduction to the ideas underlying HIV dynamic mathematical models, describe their potential utility for the design of STI strategies, and outline future directions.

2. HIV therapy

As discussed in Section 1, despite the life-saving benefits of antiretroviral therapy, the prospect of life long therapy is daunting for some HIV-infected individuals and impossible for most. Therefore, health care providers and patients are often confronted with difficult decisions regarding the advantages of initiating antiretroviral therapy while weighing the relative risks and disadvantages of long-term drug therapy.

In current clinical practice, many factors are considered in deciding when therapy should be initiated, what drugs should be used, when to change regimen and how to most effectively monitor therapeutic response. Published clinical guidelines have been established using available data and expert opinion (Yeni et al., 2004), which incorporate decision rules based on clinical, immunologic, virologic and social criteria; guidelines

issued by the U.S. Department of Heath and Human Services are available on the internet (DHHS, 2005). When considering when to start therapy, experts agree that clinical progression to AIDS or the presence of an AIDS defining illness or opportunistic infection is a clear mandate to start antiretroviral therapy. CD4 T cell counts, HIV RNA viral load measurements, and assessment of ability to comply with complex regimens are additional important variables followed in routine clinical care. Large cohort studies indicate that CD4 count as a measure of immune status is the best predictor of survival (Egger et al., 2002; Chene et al., 2003). Furthermore, patients with a baseline CD4 count between 200-350cells/mm^3 have a lower mortality rate than individuals with CD4 cell counts < 200 cells/mm^3 (Palella et al., 2003), and these patients are also at increased risk of disease progression (Sterling et al., 2003). For these reasons, recent guidelines suggest that treatment should be initiated when CD4 counts fall below 200 cells/mm^3 , and therapy should be considered when CD4 counts are between 200-350 cells/mm^3 (Yeni et al., 2004).

Whereas health care providers typically use CD4 T cell counts as a surrogate marker for staging disease, HIV RNA viral load measurements are an important predictor of rate of disease progression and a marker of therapeutic response. Natural history data from the Multicenter AIDS Cohort Study (MACS) suggest that the magnitude of viremia at viral load set-point (a plateau that is typically reached within the first 6- 12 months after acute HIV infection) is highly prognostic for the rate of disease progression (Lyles et al., 2000). In addition to viral load set-point as a prognostic factor, HIV RNA load > 100,000 copies/ml plasma is independently associated with death (Wood et al., 2003b). Based on these observations, current guidelines suggest that antiretroviral therapy should be initiated in individuals with persistently high viral load set-point, particularly those with viral load > 100,000 RNA copies/ml (Yeni et al., 2004).

CD4 T cell counts and HIV plasma viral loads often play key roles in therapeutic decision making. Although these important measures can be ascertained and followed over time, the ability to adhere to complex antiretroviral regimens is critical in determining the success of these therapies. Typical regimens consist of taking at least three drugs in combination, often requiring high pill burdens and multiple doses per day. Most individuals have difficulty complying with these types of regimens, and the consequence of noncompliance is often the elimination of therapeutic options, as drug resistance to antiretroviral medications is a large, growing issue; we discuss this further in Section 3. Along with CD4 T cell count and HIV load, in persons with pre-treatment CD4 T cell counts between 200-350 cells/mm3, adherence to antiretroviral regimen is a critical determinant of survival (Wood et al., 2003a). In patients with active substance abuse issues, the ability to adhere to these regimens is often very difficult. Therefore, biological and social factors must carefully be weighed in any decision to start antiviral therapy, as the penalty for non-compliance and persistence of viral replication can result in the systematic elimination of therapeutic options.

Once the decision to initiate antiretroviral therapy has been made, health care providers and patients need measurements that can be used to monitor therapeutic response. CD4 T cell counts and HIV RNA viral load are the most widely accepted surrogate markers for monitoring. The optimal therapeutic response would be an increase in CD4 T cells and complete suppression of HIV replication, as reflected by undetectable HIV RNA viral load (i.e., below the lower limit of quantification of the

assay). In situations where a patient may have acquired drug resistant virus, the first indicator is the emergence of persistently detectable plasma viremia, suggesting either drug resistance or non-adherence. Frequently, the re-emergence of viremia results in a slow decline in CD4 T cell counts. Therefore, viral load measurements are the cornerstone in measuring therapeutic response to antiretroviral drugs while CD4 T cell counts are the ultimate indicator of disease stage and effect of therapy. In addition to these laboratory parameters, it is common to make changes to drug regimens based on the side effects to one or more drugs in a given combination. Ultimately, it is widely recognized that tolerance to these combination regimens often determines success or failure of a treatment, with the debilitating side effects frequently limiting the ability to take these drugs.

3. Structured or supervised treatment interruption

As discussed in Section 1, the complications involved in administration of continuous HIV therapy have inspired interest in STI. Different types of STI strategies may be conceived. Some STI regimens that have been considered are *non-adaptive* in that the times at which interruption occurs and the duration of interruption prior to re-initiation of therapy are planned and hence prespecified. For example, an STI regimen may specify that antiretroviral treatment continue for 16 weeks, followed by an interruption of 8 weeks and subsequent resumption of treatment for another 16 weeks. More frequently, STI strategies are *adaptive*, wherein the decision to interrupt or re-initiate treatment is typically determined based on observation of variables such as magnitude of viremia or decline in CD4 T cell count. STI strategies of both types are heavily debated and still in early development. The clinical and biological rationale for performing cyclical treatment interruptions differs depending on stage of disease, and the optimal way to perform STI has yet to be determined.

Structured treatment interruption in individuals with chronic HIV infection has been tried with very limited success (Katlama et al., 2004; Lawrence et al., 2003; Ruiz et al., 2000; Ruiz et al., 2003; El-Sadr and Neaton, 2006). There are several rationales for interrupting therapy in patients with chronic HIV infection (Hirschel, 2001). One is to provide an individual with a break from the burden and side effects of antiretroviral therapy without negating the benefits gained from therapy. This is referred to as a "drug holiday," designed to give patients a needed respite from the burden of continuous therapy and the accompanying side effects.

Planned treatment interruption has also been performed in individuals with multi-drug resistant HIV. The rationale for discontinuing therapy in this situation is to allow "wild-type," drug sensitive viral quasi-species to repopulate the body and preferentially replicate over less susceptible, drug resistant virus. Lengthy therapy with antiretroviral agents may result in the emergence of drug resistant virus, which is particularly likely if a patient is poorly adherent with a given drug regimen. The development of drug resistance may have significant clinical consequences, as it may eliminate an entire drug class (or classes), limiting the number of drug options and creating difficult management challenges. However, genotypic mutations, which alter susceptibility to antiretroviral therapy, may in theory "cost" the virus in terms of its "fitness" or ability to replicate

(Croteau et al., 1997; Deeks et al., 2001; Nijhuis et al., 2001).   Some studies have shown that cessation of antiviral therapy results in a reversion of viral quasi-species back to wild-type virus. These observations have given rise to the hypothesis that an interruption in therapy eliminates drug pressure resulting in reversion of viral populations to a more susceptible viral quasi-species, therefore improving chances that subsequent salvage regimens will be effective. Although studies have demonstrated that virus harboring genotypic mutations can revert back to wild-type quasi-species and may improve virologic outcome (Katlama et al., 2004), this strategy has so far failed to produced clinical benefit and in general is not recommended in routine practice (Antinori et al., 2005; Ghosn et al., 2005; Yeni et al., 2004).

Acute HIV infection is defined as the period from viral entry to formation and detection of HIV-specific antibodies. This time period immediately following establishment of viral infection may offer an opportunity to initiate therapy with the goal being preservation of HIV-specific immunity and treatment discontinuation (Kassutto and Rosenberg 2004; Rosenberg et al., 1997; Rosenberg et al., 2000). The rationale for this approach is grounded in the biologic and immunologic events surrounding primary HIV infection. A hallmark of acute HIV infection is the extreme degree of viral replication resulting in high levels of viremia. One unique feature of this infection is that virus preferentially targets and infects HIV-specific CD4+ T helper (Th) cells (Douek et al., 2002), resulting in a profound impairment in their function. HIV-specific T helper cells are believed to be critical in the normal generation and maintenance of effective cellular and humoral immune responses. One hypothesis is that treatment with antiretroviral therapy during acute HIV infection will limit viral replication and minimize the impairment of HIV-specific T helper cells. Early treatment during acute HIV infection reliably restores HIV-specific Th cells that would otherwise be lost (Oxenius et al., 2000; Rosenberg et al., 1997; Rosenberg et al., 2000), resulting in an immunological phenotype similar to that of individuals with long-term non-progressive (LTNP) infection (Rosenberg et al., 1997). The difference is that persons with LTNP HIV infection spontaneously control viral replication in the absence of antiretroviral therapy whereas individuals treated during acute HIV infection require therapy to contain viremia.

Given the immunological similarities observed in persons treated during acute HIV infection and individuals with LTNP infection, investigators have been questioning whether immune responses that are generated and maintained during treatment of acute infection would be adequate enough to control viral replication if therapy is discontinued. Anecdotal evidence suggests that viremia returns once therapy is discontinued but viral load set-point may be lower (Lisziewicz et al., 1999; Rosenberg et al., 2000). These observations have subsequently generated additional questions. For example, can cyclical or structured interruptions of therapy resulting in re-exposure to autologous virus further stimulate and augment host immune responses? If so, will these enhanced immune responses result in improved antiviral control with each successive interruption in therapy? This concept of "autologous vaccination" via STI has been attempted in very limited trials with mixed success. It appears that in persons undergoing STI, there is immunological control of viral replication but the duration is transient (Rosenberg et al., 2000; Kaufmann et al., 2004). These mixed results indicate that the best way to manage persons with acute HIV infection is not known, and it is unclear whether treatment interruption in this setting has any benefit.

It is clear that further investigation is needed to determine whether STI should be performed and, if so, what strategy will produce the best results. Notably, studies of STI in the context of acute infection have been limited by small sample size and, importantly, by a lack of reliable information on how to design interruption strategies. It is evident that a potentially unlimited number of practically feasible STI strategies, both non-adaptive or adaptive, may be conceived, raising the possibility that those studied so far, whose specific decision rules were developed on the basis of expert opinion and "educated guesses," may have been unfortunately chosen. Given the complexity of HIV infection and the existing guidelines for HIV treatment discussed in Section 2 that dictate that treatment be introduced or modified according to status of clinical, immunological, and virologic criteria, STI regimens for which the decisions on interruption and re-initiation of treatment are made adaptively hold the most promise. That is, the most promising STI strategies are likely to be *adaptive treatment strategies*. This suggests that emerging advances for the formulation of adaptive treatment strategies, including experimental designs to collect appropriate data for this purpose (e.g., Collins et al., 2004; Lavori and Dawson, 2003; Murphy, 2005; Murphy et al., 2005) could be exploited, providing a systematic, principled basis for constructing STI strategies.

As noted in Section 1, hypotheses about the biology of HIV infection may be operationalized through HIV dynamic models, which are mathematical descriptions of the mechanisms underlying the interaction between virus and immune system and the effects of treatment on these processes within a patient. Thus, in the HIV context, these mathematical models offer a unique, alternative basis for constructing adaptive (as well as non-adaptive) STI treatment strategies.

4. HIV dynamic models

HIV dynamic models are based on representing processes involved in the virus-immune system interplay through a series of hypothetical "compartments" characterizing different populations of virus and constituents of the immune system. The collection of compartments so hypothesized is regarded as a "system" within the patient in which interactions take place among the populations in the various compartments over time.

One compartment usually included in these models is the population of infectious virus particles, or virions, present in the body. Typical other compartments include the population of non-infected CD4 T cells, which are targets for infection by virus; the population of infected CD4 T cells, those that have already been infected by the virus; the population of non-infectious virus (e.g., virus that has been rendered incapable of infecting T cells via the effect of treatment); and populations of other cells that are involved in the immune system's "counterattack" against the virus (e.g., cytotoxic T-lymphocytes, or CTLs, which are produced in response to the presence of infected cells). Over time, the size of the population in each compartment is assumed to change according to specific assumptions about how the virus interacts with the other populations. For example, it might be assumed that infectious viral particles infect non-infected target CD4 T cells at a constant rate per unit of time. When a CD4 T cell is infected, the virus uses it as a vehicle to replicate itself; thus, such infection causes more infectious viral particles to be produced and leads to the death of the infected T cell when

the new viral particles produced are released. A model may suppose that these infected cells produce new infectious virions at a certain rate per unit time and then die at some rate. Virus also dies naturally; thus the model may assume that virus particles exit the "system" at some rate. One may make different assumptions about the number of compartments present and how they interact, which lead to different overall representations of the mechanisms thought to be occurring in HIV infection within a patient. With more compartments and interactions, models may be made more compatible with hypotheses about what are undoubtedly rather complicated biological processes.

Treatment may also be introduced into the "system." The different antiretroviral agents that comprise typical combination therapy include reverse transcriptase inhibitors (RTI), which act to block new infections, and protease inhibitors (PI), which cause infected T cells to produce non-infectious virus. These effects are often incorporated by assuming that, for example, in the presence of RTI therapy, the rate of production of new infectious virus is attenuated by some constant factor. The models can accommodate changes in the "input" of treatment into the system; e.g., treatment may be "turned on" or "off" over time. This feature may be exploited in the design and study of different STI strategies, elaborated in the next section.

Fig. 1 presents a schematic of a typical and fairly simple model. The model includes compartments for the populations of infected and non-infected CD4 T cells, which, when uninfected, are the main target for the virus and, when infected, are the main source of viral replication; and compartments for infectious and non-infectious virus populations. Also included are compartments representing infected and non-infected so-called CD4 memory cells, which may be thought of as a "latent" population of CD4 cells that become infected and die at different rates from the main populations. These memory compartments represent in a simple way the belief that there is a reservoir of target cells that lie in a latent state in which they do not produce new virus, and are responsible for the fact that the virus always can reemerge upon withdrawal of therapy. The arrows labeled "differentiation" indicate that target CD4 T cells may revert to latent status, becoming part of the reservoir, and the "activation" arrows allow latent cells to emerge and contribute to the main target population and, if infected, production of virus. The "immune effectors" compartment represents CTL cells that arise from the presence of infected CD4 T cells, indicated by the arrow pointing from the infected CD4 T cell compartment. These cells are part of the response of the immune system; the upper arrow pointing away from this compartment represents their action in killing infected CD4 cells. The arrows emerging from the infectious virus compartment depict hypothesized actions of the virus in stimulating and infecting CD4 cells; the "RTI" notation represents the effect of these therapeutic agents at interfering with the ability of the virus to transform non-infected target cells to infected status. The arrow from the infected CD4 compartment to the infectious virus compartment represents the release of new virus produced by infection; the arrow pointing to the non-infectious virus compartment with the "PI" notation incorporates the effect of protease inhibitors in leading to production of non-infectious virus. For all compartments, the outward arrows with no destination represent death of the cells in the respective populations.
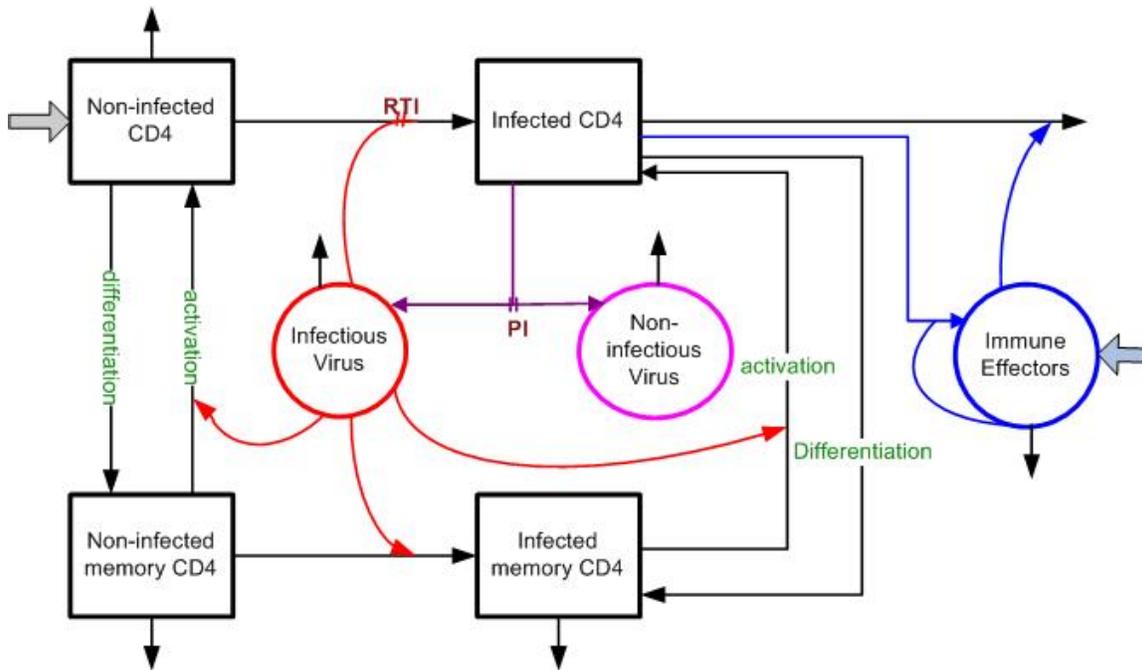
Fig 1. Schematic diagram of a typical HIV dynamic model. The model has seven compartments representing infectious and non-infectious virus, infected and non-infected CD4 T cells, infected and non-infected latent memory CD4 T cells, and cytotoxic T-lymphocytes (CTLs) (immune effectors).   The arrows depict interactions among the compartments; for example, the arrow from the non-infected CD4 compartment to the infected CD4 compartment indicates the transformation of the former type of cells to the latter as they are infected by infectious virus. The "RTI" notation represents the effect of reverse transcriptase inhibitors in interfering with the infection process.   Further description of the components of the model is given in the text

Once the compartmental depiction is conceived, it may be formulated mathematically as a system ordinary differential equations, or ODEs, in terms of variables that represent the size of the population in each compartment at each point in time, where time "0" represents the time at which virus is introduced into the body (i.e., the time of infection), and a set of "initial conditions" corresponding to the state of the system at time 0. The ODEs formalize how each variable changes as the hypothesized processes of infection of target cells, production of new virus, stimulation of the immune system, and viral and cell death take place over time.   Given a set of "initial conditions" formalizing the belief about the state of the system at time 0, the system of ODEs may be solved to yield, ideally, expressions for the size of the populations in each compartment at any time in terms of the rates of infection, production, death, etc., and, in the presence

of antiretroviral therapy, the assumed efficacies of the various agents (e.g., RTI and PI) given in combination. In simplistic models with only a few compartments, these expressions may be written down explicitly, so that an equation that gives, e.g., the concentration of infectious virus in the body at any time is available. However, when the model is simple enough to permit such explicit expressions, it is usually also too simple to provide a realistic approximation to the true set of complex mechanisms governing HIV pathogenesis. For models including more compartments that offer more realistic approximations, such explicit expressions are typically impossible to derive. However, the numerical value for the size of the population in any compartment at any time may be obtained using sophisticated "ODE solver" software (e.g., Hairer et al., 1996; Hindmarsh, 1983).

An HIV dynamic model thus describes the processes taking place over time within an HIV-infected individual under a specific set of assumptions on the virus-immune system interaction and the effects of treatment. It is natural to expect that, although the processes so represented might be similar for different patients, they would not be identical because of the natural biological heterogeneity that is expected across individuals as well as due to identifiable characteristics of patients (e.g., gender, comorbidities, behavioral factors). This is conceptualized by supposing that, while each patient follows the same system of ODEs, the values of the rates of infection, viral production, cell and viral death; the effects of treatment; and so on, are different for different patients. For convenience, we refer to these quantities henceforth as the "model parameters." The same system of ODEs will behave differently with different values of the model parameters. Thus, if the values of model parameters differ across patients, this would lead to, for example, different patients undergoing the same treatment regimen to exhibit different responses (e.g., HIV RNA viral load and CD4 T cell counts over time). From this perspective, then, taking a particular HIV dynamic model as an approximation to the processes taking place inside patients, the extent to which the values of the model parameters vary across patients dictates the extent to which clinical outcomes vary across patients, a feature that may be exploited in the design of STI strategies, as described in the next section.

In actual patients, all of the compartments that make up a realistic such HIV dynamic model cannot be observed; typically, HIV RNA viral load and CD4 T cell count are the standard measurements taken on a patient, as discussed in Section 2. In the context of the dynamic model, for example, as viral assays cannot distinguish infectious and non-infectious virus, HIV RNA viral load may be viewed as a measurement of the sum of the sizes of the populations in the infectious and non-infectious virus compartments.

Thus, although very complicated, realistic models can be conceived, information on only some of the model components is available clinically. Nonetheless, given frequent clinical longitudinal observations of, say, HIV RNA viral load and CD4 T cell count, on a patient, it is possible using advanced mathematical and statistical techniques (Banks and Kunisch, 1989; Davidian and Giltinan, 1995, 2003; Kelley, 1999; Vogel, 20002) to learn about the values of his/her underlying model parameters. More formally, the model parameters may be *estimated* for each patient based on his/her longitudinal data via principled statistical inference techniques. Once the parameters are estimated, using numerical techniques mentioned above, the system may be "solved" using the

estimated values of the parameters to yield the values of, e.g., HIV RNA viral load and CD4 T cell count predicted by the model at any time. Fig. 2 depicts predictive model fits for these measures obtained from the data from a patient acutely infected with HIV under a model similar to that in Fig. 1, where the fits have been superimposed on the actual longitudinal observations from the patient. The thick solid lines on the horizontal axis indicate time periods where the patient was undergoing antiretroviral therapy. The fit of the model tracks the overall progression of CD4 T cell count (a) and HIV RNA viral load (b) well in light of the "noise" present, particularly in the former measurements, accurately predicting the long term trend toward decline in CD4 T cell count. Working with HIV RNA viral load measurements is complicated by the fact that, under therapy, these tend to drop below the lower limit of quantification of the viral load assay, so that their actual values are known only to lie below this limit. Such values of viral load are plotted in Fig. 2(b) at the value of the known limit of quantification. Fitting the model involves the additional complication of taking this feature into account, which has been carried out here by combining the usual estimation techniques mentioned above with methods for regression analysis for such so-called "censored" data, described in this context by Adams et al. (2006). The open circles in Fig. 2(b) indicate model-based estimates of the actual values of viral load that would have been observed had there been no assay limit of quantification at the time points where viral load values were censored by the limit.
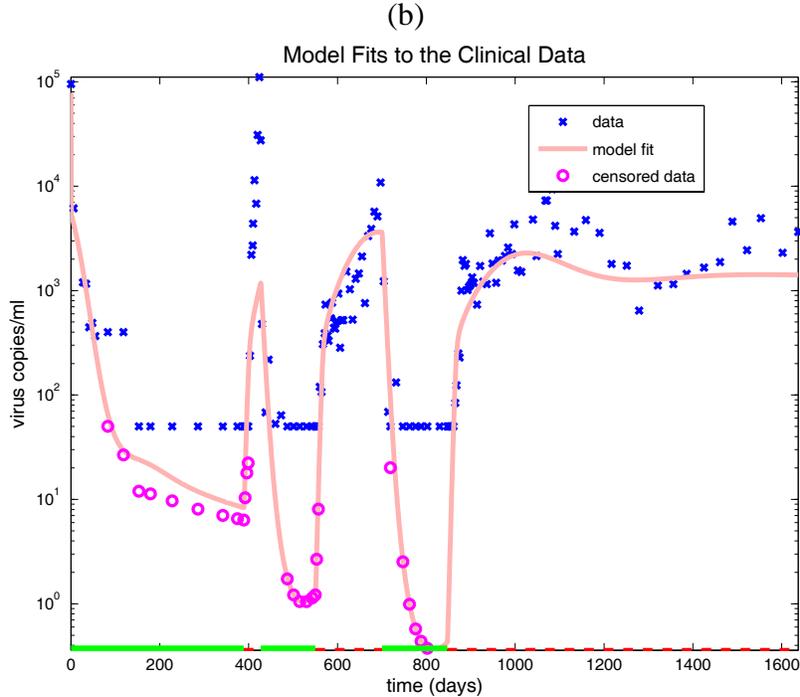
(a)

10

(b)

Model Fits to the Clinical Data
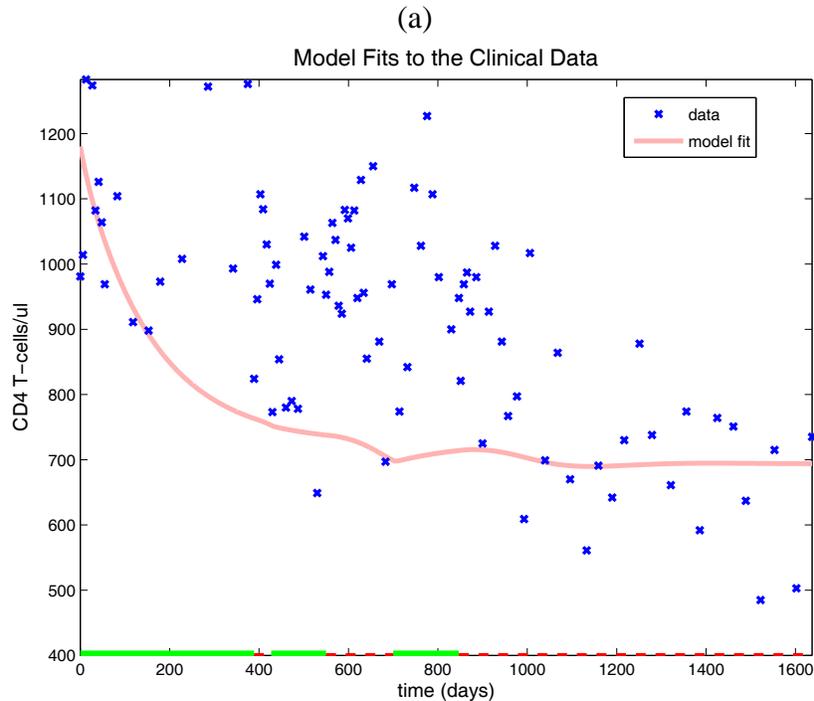
Fig 2. (a) Estimated time profile of CD4 counts from fitting a model similar to that depicted schematically in Fig. 1 to longitudinal data from a patient acutely-infected with HIV. The thick bars on the horizontal time axis correspond to time intervals when the patient was on antiretroviral therapy; note that this patient permanently interrupted therapy at about 825 days. (b) Estimated time profile of HIV RNA viral load from the same model fit as in (a). During the time on treatment, viral load values drop below the lower limit of quantification of the assay; viral load is plotted in this case at the lower limit. The fit of the model takes into account this "censoring" of viral loads, with the open circles representing "estimates" of the values of viral load under these conditions.

When longitudinal data from a sample of patients are available, estimates of the model parameters for each may be deduced using these methods, and these may be used collectively to construct via formal and informal statistical methods a representation of the way in which the parameters vary in the entire population. That is, this representation may be achieved by identifying and estimating a *probability distribution* that approximates how the model parameters vary in the population. As we now discuss, this, along with further mathematical advances, holds promise for facilitating the design of STI regimens.

5. Design of STI strategies using HIV dynamic models

The availability of HIV dynamic models and information from data on the associated model parameters for individual patients or samples of patients suggests the use of a powerful mathematical tool that can offer guidance on the design of both non-

adaptive and adaptive STI treatment strategies. *Control theory* is a body of mathematical theory and techniques for modifying the behavior of systems of ODEs like HIV dynamic systems through the control of system inputs (Anderson and Moore, 1990; Camacho and Bordons, 2004). Here, the input is potent antiretroviral therapy; as noted previously, STI involves turning the input "on" or "off" at various points over time. Control theory seeks to specify the best strategies for controlling the treatment input over time for a particular model in order to optimize a particular objective. For example, the objective may be to drive viral load set-point to a value below a specified low threshold while minimizing the burden imposed on patients under treatment. Such objectives may be formalized mathematically, and control theory may then be used to derive input strategies over time that achieve the objective.

Two types of control theory are available. *Open loop* control does not use "feedback" from the system over time to deduce the input as a function of time. That is, open loop control involves specifying a sequence of inputs to the system that will be followed regardless of how the system responds to the inputs. Thus, in the context of STI, open loop control theory can only be used to design what we have referred to previously as non-adaptive STI regimens for which the times at which treatment will be interrupted and reinstated would be pre-planned to take place regardless of how the patient was doing i.e., the decision rules for interrupting and reinitiating treatment do not depend on the current state of the patient.

Open loop control inputs are relatively easy to derive mathematically, but open loop control is not directly useful for the goal of designing STI strategies that are adaptive. From a mathematical perspective, construction of adaptive strategies requires the use of theory for what is known as *feedback control*. Feedback control theory takes into account the current state of the system in determining the inputs over time to optimize a specific objective. In the context of STI, feedback control methods would result in strategies that involve decision rules for interrupting treatment (or not) based on past and current values of HIV RNA viral load and CD4 count; i.e., adaptive treatment. Not surprisingly, the mathematical derivation of feedback control strategies is more complicated than that for open loop control. One difficulty with classical feedback control theory is that it can lead to treatment strategies that are not practically feasible; e.g., requiring measurements from patients according to schedules that are not realistic in practice. Modifications of feedback control theory to result in more feasible treatment input strategies have been suggested (Adams et al., 2004, 2005; Banks et al., 2005b; Camacho and Bordons, 2004; Limon et al., 2002; Magni et al., 2001) and are currently in development for specific use in designing practical STI regimens for HIV treatment.

Both open loop and feedback control theoretic methods have been used theoretically in the HIV context to suggest "optimal" strategies for administering antiretroviral therapy over time (Adams et al., 2004, 2005; Banks et al., 2005a; Brandt and Chen, 2001; Culshaw et al., 2004; Jeffrey et al., 2003; Kirschner et al., 1997; Wein et al., 1997). For example, in Adams et al. (2005), the authors considered a fairly complicated HIV dynamic model and used open loop control theory to design STI strategies that involve a short-term pattern of several interruptions after infection. They showed that such strategies can, at least theoretically, lead to long-term control of the virus in some patients. However, to the knowledge of the authors, HIV dynamic models and this theory have mainly been used to deduce and study STI strategies hypothetically

but have not been used in a systematic way to design STI strategies with the intention of implementing them in actual clinical trials. We now outline how we envision that HIV dynamic models, control theory, and information from data on the values of both model parameters and the probability distribution that describes how they vary across patients may be used for this purpose.

Under the assumption that a particular HIV dynamic model is a reasonable approximation to the processes underlying HIV disease within a patient, longitudinal data from existing patients may be used to estimate the model parameters for single patients and thus to approximate the probability distribution describing variation in the population of patients using sophisticated mathematical and statistical methods This facilitates the ability to *simulate* an entire population of "virtual patients" resembling the true population of existing patients. Specifically, a virtual patient may be simulated by randomly generating from the probability distribution a set of model parameters corresponding to the patient. This may be carried out repeatedly to produce a large number of patients. As discussed in Section 4, the values of the model parameters for a virtual patient will dictate how, for example, that patient's HIV RNA viral load and CD4 count would evolve over time under different treatment strategies.

Given the values of model parameters, control theory (preferably feedback control theory modified to result in practically feasible treatment inputs) may be used to derive promising STI strategies. A particular strategy may then be "followed" by each virtual patient, yielding from the dynamic model under the strategy the values of viral load and CD4 count at any time for the patient under the strategy. The results from many such virtual patients may be combined to provide a hypothetical picture of how the population of HIV-infected patients would fare if all were to follow the particular STI treatment strategy under consideration.

As a simple example, Fig. 3 presents HIV RNA viral load profiles generated for 100 such virtual patients who "followed" the simple non-adaptive STI strategy of starting antiretroviral therapy at time 0, with a terminal (no subsequent re-initiation of therapy) interruption of therapy at 6 months.   The profiles for all 100 patients were simulated from the same HIV dynamic model; however, as noted above, each patient had a different setting of the model parameters (randomly generated from the probability distribution for each). Similar to the behavior for the real patient in Fig. 2(b), continuous treatment until six months results in very low viral load; when treatment is withdrawn at six months, all patients exhibit a rebound in viral load that eventually stabilizes at a set-point for each. The figure shows clearly how, although they all underwent the identical treatment strategy, patients vary considerably in the extent and steepness of decline in viral load under therapy and the eventual set-point to which their viral load stabilizes, reflecting the different values of their underlying model parameters.
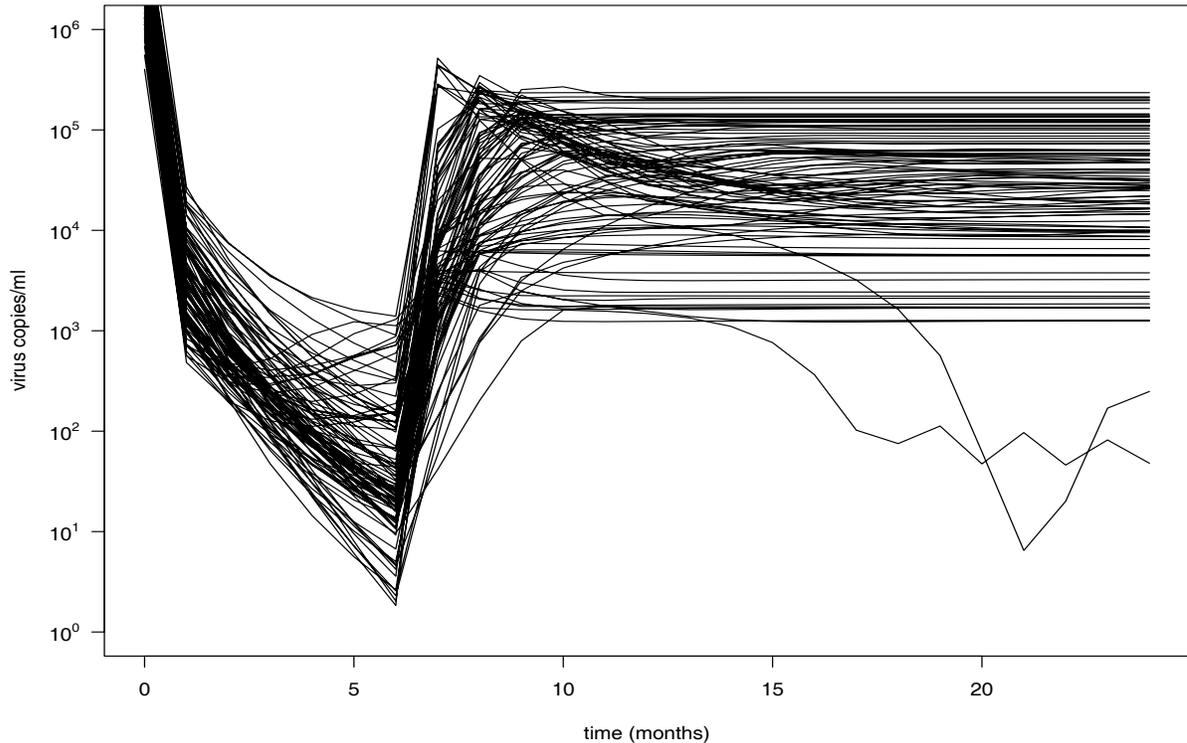
Fig 3. HIV RNA viral load time profiles for 100 "virtual patients." All profiles are based on the same HIV dynamic model, similar to that depicted in Fig. 1. To create a virtual patient, values of the model parameters were randomly generated from a probability distribution representing how the model parameters vary in the population of patients. The system of ordinary differential equations was then solved using this value of the model parameters to yield the time profile for that patient.

Such simulations have the potential to provide valuable insight into the relative benefits of different STI strategies based on, say, different objectives, different HIV dynamic models, and different assumptions about the population. As patients would naturally vary in their responses, the results from numerous "virtual patients" would provide important information on the extent to which the benefits of a strategy vary across patients as well. The facility to simulate "virtual patients" means that numerous strategies could be studied, albeit hypothetically, in real time without the commitment of actual patients or resources.

Of course, the advantages of using mathematical modeling and control theory in this way can only be confirmed through testing of the STI strategies so derived in actual

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patients. The authors of this paper are part of a multidisciplinary team that is currently using these tools to develop STI regimens for the treatment of acutely-infected patients. The most promising of these strategies will be studied in a clinical trial. An important component of the trial will be to collect detailed, frequent longitudinal data on not only HIV RNA viral load and CD4 counts in order to measure response to the treatment, but also on other potentially important measures, such as measurements on cytotoxic T-lymphocytes and the "fitness" of the virus. These rich data will contain critical information that will form the basis for suggesting improvements to the mathematical HIV dynamic model to render it more clinically relevant. These data may also be used to estimate model parameters and probability distributions of model parameters that may be used to design improved STI strategies based on the improved model.

Summarizing, we envision that the availability of these mathematical and statistical tools could lead to an iterative approach to the clinical study of HIV infection and the development of STI treatment strategies through a series of small, proof-of-principle studies. The strategy would proceed as follows. Existing data could be used to guide development of HIV dynamic model development and estimation of model parameters and their probability distribution. These could be combined with control theoretic methods to suggest new STI strategies that could then be evaluated by simulated application to the "virtual" target population. The most promising might be incorporated in a clinical trial, the data from which would both provide information on the benefits of the strategies studied and inform refinements to the model that may in turn be exploited to design new strategies. Strategies emerging from this sequence of trials would be worthy candidates for testing against more conventional treatment regimens in large confirmatory trials.

6. Discussion

The goal of this paper is to promote the idea that, when available, mathematical models for biological mechanisms involved in disease, coupled with advanced statistical methods for their application to data, may be a valuable tool for assisting in the design of adaptive treatment strategies. Because of the wealth of research on HIV pathogenesis and HIV dynamic models formalizing description of its underlying processes, the development of STI regimens for HIV infection is a key setting where we believe that this approach is both feasible and has great potential. In a future report, we will recount our experience implementing the ideas presented in this paper in the HIV context. We hope that the ideas reviewed herein will inspire consideration of mathematical-statistical models as a potential tool for guiding the conception of adaptive treatment strategies in other settings where this is possible.

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References

Adams, B.M., Banks, H.T., Kwon, H.D., Tran, H.T. , 2004. Dynamic multidrug therapies for HIV: Optimal and STI control approaches. Math. Biosci. Eng. 1, 223-242.

Adams, B.M., Banks, H.T., Davidian, M., Kwon, H.D., Tran, H.T., Wynne, S.N., Rosenberg, E.S., 2005. HIV dynamics: Modeling, data analysis, and optimal treatment protocols. J. Comp. Appl. Math. 184, 10-49.

Adams, B.M., Banks, H.T., Davidian, M., Rosenberg, E.S. 2006. Model fitting and prediction with HIV treatment interruption data. Submitted.

Anderson, B.D.O., Moore, J.B., 1990. Optimal Control: Linear Quadratic Methods. Prentice Hall, Englewood Cliffs, New Jersey.

Antinori, A., Cingolani, A., Perno, C.F., 2005. Structured treatment interruption in HIV-infected patients failing on multidrug therapy: is there a future for this strategy? AIDS 19, 1691-1694.

Banks, H.T., Kunisch, K., 1989. Estimation Techniques for Distributed Parameter Systems. Birkhauser, Boston.

Banks, H.T., Kwon, H.D., Toivanen, J.A., Tran, H.T., 2005a. An SDRE based estimator approach for HIV feedback control. J. Opt. Cont. Appl.Math., in press.

Banks, H.T., Lewis, B.M., Tran, H.T., 2005b. Nonlinear feedback controllers and compensators: A state-dependent Riccati equation approach. Comp. Opt. Appl. , in press.

Brandt, M.E., Chen, G., 2001. Feedback control of a biodynamical model of HIV-1. IEEE Trans.Biomed. Eng. 48, 754-759.

Camacho, E.F., Bordons, C., 2004. Model Predictive Control. Springer-Verlag, London.

Chen, R.Y., A. O. Westfall, et al., 2003. Duration of highly active antiretroviral therapy regimens. Clin. Infect. Dis. 37, 714-722.

Chene, G., J. A. Sterne, et al., 2003. Prognostic importance of initial response in HIV-1 infected patients starting potent antiretroviral therapy: analysis of prospective studies. Lancet 362, 679-686.

Collins, L.M., Murphy, S.A., Bierman, K.L., 2004. A conceptual framework for adaptive preventive interventions. Prev. Sci. 5, 185-196.

Croteau, G., L. Doyon, et al., 1997. Impaired fitness of human immunodeficiency virus type 1 variants with high-level resistance to protease inhibitors. J. Virol. 71, 1089-1096.

Culshaw, R.V., Ruan, S., Spiteri, R.J., 2004. Optimal HIV treatment by maximising immune response. J. Math. Bio. 48, 545-562.

Davidian, M., Giltinan, D.M., 1995. Nonlinear Models for Repeated Measurement Data. Chapman and Hall/CRC Press, New York.

Davidian, M., Giltinan, D.M., 2003. Nonlinear models for repeated measurement data: An overview and update. J. Agricult. Bio. Env. Statist. 8, 387-419.

Deeks, S.G., Wrin, T., Liegler, T., Hoh, R., Hayden, M., Barbour, J.D., Hellmann, N.S., Petropoulos, C.J., McCune, J.M., Hellerstein, M.K., Grant, R.M., 2001. Virologic and immunologic consequences of discontinuing combination antiretroviral-drug therapy in HIV-infected patients with detectable viremia. N. Engl. J. Med. 344, 472-480.

Detels, R., Munoz, A., McFarlane, G., Kingsley, L.A., Margolick, J.B., Giorgi, J., Schrager, L.K., Phair, J.P, 1998. Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. Multicenter AIDS Cohort Study Investigators. JAMA 280, 1497-1503.

DHHS, 2005. U.S. Department of Health and Human Services Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at http://www.aidsinfo.nih.gov, last accessed 4/3/06.

Di Mascio, M., Riberio, R.M., Markowitz, M., Ho, D.D., Perelson, A.S. 2004. Modeling the long-term control of viremia in HIV-1 infected patients treated with antiretroviral therapy. Math. Biosci. 188, 47-62.

Dixit, N.M, Perelson, A.S., 2004. Complex patterns of viral load decay under antiretroviral Erhart: Influence of pharacokinetics and intracellular delay. J. Theor. Bio. 226, 95-109.

Douek, D.C., Brenchley, J.M., Betts, M.R., Ambrozak, D.R., Hill, B.J., Okamoto, Y., Casazza, J.P., Kuruppu, J., Kunstman, K., Wolinsky, S., Grossman, Z., Dybul, M., Oxenius, A., Price, D.A., Connors, M., Koup, R.A., 2002. HIV preferentially infects HIV-specific CD4+ T cells. Nature 417, 95-98.

Egger, M., May, M., Chene, G., Phillips, A.N., Ledergerber, B., Dabis, F., Costagliola, D., D'Arminio Monforte, A., de Wolf, F., Reiss, P., Lundgren, J.D., Justice, A.C., Staszewski, S., Leport, C., Hogg, R.S., Sabin, C.A., Gill, M.J., Salzberger, B., Sterne, J.A., 2002. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet 360, 119-129.

El-Sadr, W. and Neaton, J. for the SMART Investigators, 2006. Episodic CD4-guided use of ART is inferior to continuous therapy: Results of the SMART study. Abstract #106LB, 13th Conference on Retroviruses and Opportunistic Infections, Denver CO, February 2006.

Finzi, D., Blankson, J., Siliciano, J.D., Margolick, J.B., Chadwick, K., Pierson, T., Smith, K., Lisziewicz, J., Lori, F., Flexner, C., Quinn, T.C., Chaisson, R.E., Rosenberg, E., Walker, B., Gange, S., Gallant, J., Siliciano, R.F., 1999. Latent infection of CD4+ T cells provides a mechanism for lifelong persistence of HIV-1, even in patients on effective combination therapy. Nat. Med. 5, 512-517.

Ghosn, J., Wirden, M., Ktorza, N., Peytavin, G., Ait-Mohand, H., Schneider, L., Dominguez, S., Bricaire, F., Calvez, V., Costagliola, D., Katlama, C., 2005. No benefit of a structured treatment interruption based on genotypic resistance in heavily pretreated HIV-infected patients. AIDS 19, 1643-1647.

Hairer, E., Wanner, G., 1996. Solving Ordinary Differential Equations. II. Stiff and Differential-Algebraic Problems, vol. 14, Springer Series in Computational Mathematics (2nd edition). Springer-Verlag, Berlin.

Hindmarsh, A.C., 1983. Scientific Computing, Chapter on ODEPACK, A systematized collection of ODE solvers, pp. 55-64. North Holland, New York.

Hirschel, B., 2001. Planned interruptions of anti-HIV treatment. Lancet Infect. Dis. 1, 53-59.

Ho, D.D., Neumann, A.U., Perelson, A.S., Chen, W., Leonard, J.M., Markowitz, M., 1996. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. Nature 373, 123-126.

Jeffrey, A.M., Xia, X., Craig, I.K., 2003. When to intiate HIV therapy: A control theoretic approach. IEEE Trans. Biomed. Eng. 50, 1213-1220.

Kassutto, S., Rosenberg, E.S., 2004, Primary HIV type 1 infection. Clin. Infect. Dis. 38, 1447-1453.

Katlama, C., S. Dominguez, et al., 2004. Benefit of treatment interruption in HIV-infected patients with multiple therapeutic failures: a randomized controlled trial (ANRS 097). AIDS 18, 217-226.

Kaufmann, D.E., Lichterfeld, M., Altfeld, M., Addo, M.M., Johnston, M.N., Lee, P.K., Wagner, B.S., Kalifer, E., Strick, D., Rosenberg, E.S., Walker, B.D., 2004. Limited durability of viral control following treated acute HIV infection. PLoS Med 1, e36.

Kelley, C.T., 1999. Iterative Methods for Optimization. Frontiers in Applied Mathematics FR18. SIAM, Philadelphia.

Kirscher, D., Lenhart, S., Serbin, S., 1997. Optimal control of the chemotherapy of HIV. J. Math Bio. 35, 775-792.

Lavori, P.W., Dawson, R., 2003. Dynamic treatment regimes: practical design considerations. Clin. Trials 1, 9-20.

Lawrence, J., Mayers, D.L., Hullsiek, K.H., Collins, G., Abrams, D.I., Reisler, R.B., Crane, L.R., Schmetter, B.S., Dionne, T.J., Saldanha, J.M., Jones, M.C., Baxter, J.D., (2003). "Structured treatment interruption in patients with multidrug-resistant human immunodeficiency virus." N Engl J Med 349, 837-846.

Ledergerber, B., Egger, M., Opravil, M., Telenti, A., Hirschel, B., Battegay, M., Vernazza, P., Sudre, P., Flepp, M., Furrer, H., Francioli, P., Weber, R., 1999. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study. Swiss HIV Cohort Study. Lancet 353, 863-868.

Limon, D., Alamo, T., Camacho, E.F., 2002. Enlarging the domain of attraction of MPC controller using invariant sets. Proceedings of the IFAC World Congress.

Lisziewicz, J., E. Rosenberg, et al., 1999. Control of HIV despite the discontinuation of antiretroviral therapy. N. Engl. J. Med. 340, 1683-1684.

Lori, F., Lewis, M.G., Xu, J., Varga, G., Zinn, D.E., Crabbs, C., Wagner, W,, Greenhouse, J., Silvera, P., Yally-Ogunro, J., Tinelli, C., Lisziewicz. J., 2000. Control of SIV rebound through structured treatment interruptions during early infection. Science 290, 1591-1593.

Lori, F., Lisziewicz , J., 2001. Structured treatment interruptions for the management of HIV infection. JAMA 286, 2981-2987.

Lyles, R. H., Munoz, A., Yamashita, T.E., Bazmi, H., Detels, R., Rinaldo, C.R., Margolick, J.B., Phair, J.P., Mellors, J.W., for the Multicenter AIDS Cohort Study, 2000. Natural history of human immunodeficiency virus type 1 viremia after seroconversion and proximal to AIDS in a large cohort of homosexual men. Multicenter AIDS Cohort Study. J. Infect. Dis. 181, 872-880.

Magni, L., DeNicolao, G., Magnani, L., Scattolini, R., 2001. A stabilizing model based predictive control algorithm for nonlinear systems. Automatica 37, 1351-1362.

Martinez, E., Mocroft, A., Garcia-Viejo, M.A., Perez-Cuevas, J.B., Blanco, J.L., Mallolas, J., Bianchi, L., Conget, I., Blanch, J., Phillips, A., Gatell, J.M.,, 2001. Risk of lipodystrophy in HIV-1-infected patients treated with protease inhibitors: a prospective cohort study. Lancet 357, 592-598.

Murphy, E.L., Collier, A.C., Kalish, L.A., Assmann, S.F., Para, M.F., Flanigan, T.P., Kumar, P.N., Mintz, L., Wallach, F.R., Nemo, G.J., et al., 2001. Highly active antiretroviral therapy decreases mortality and morbidity in patients with advanced HIV disease. Ann. Intern. Med. 135, 17-26.

Murphy, S.A., 2005. An experimental design for the development of adaptive treatment strategies. Statistics in Medicine 24, 1455-1481.

Murphy, S.A., Olsin, D., Rush, A.J., Zhu, J., 2005. Methodological challenges in constructing effective treatment sequences for chronic disorders. Submitted.

Nijhuis, M., S. Deeks, et al., 2001. Implications of antiretroviral resistance on viral fitness. Curr. Opin. Infect. Dis. 14, 23-28.

Notermans, D.W., Goudsmit, J., Danner, S.A., 1998. Rate of HIV-1 decline following antiretroviral therapy is related to viral load at baseline and drug regimen. AIDS 12, 1483-1490.

Oxenius, A., Price, D.A., Easterbrook, P.J., O'Callaghan, C.A., Kelleher, A.D., Whelan, J.A., Sontag, G., Sewell, A.K., Phillips, RE., 2000. Early highly active antiretroviral therapy for acute HIV-1 infection preserves immune function of CD8+ and CD4+ T lymphocytes. Proc. Natl. Acad. Sci. U S A 97, 3382-3387.

Palella, F.J., Jr., Delaney, K.M., Moorman, A.C., Loveless, M.O., Fuhrer, J., Satten, G.A., Aschman, D.J., Holmberg, S.D, 1998. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N. Engl. J. Med. 338, 853-860.

Palella, F.J., Jr., Deloria-Knoll, M., Chmiel, J.S., Moorman, A.C., Wood, K.C., Greenberg, A.E., Holmberg, S.D., 2003. Survival benefit of initiating antiretroviral therapy in HIV-infected persons in different CD4+ cell strata. Ann. Intern. Med. 138, 620-626.

Perelson, A S., Essunger, P., Cao, Y.Z., Vesanen, M., Hurley, A., Saksela, K., Markowitz, M., Ho, D.D., 1997. Decay characteristics of HIV-1-infected compartments during combination therapy. Nature 387, 188-191.

Phillips, A.N., Dunn, D., Sabin, C., Pozniak, A., Matthias, R., Geretti, A.M., Clarke, J., Churchill, D., Williams, I., Hill, T., Green, H., Porter, K., Scullard, G., Johnson, M., Easterbrook, P., Gilson, R., Fisher, M., Loveday, C., Gazzard, B., Pillay, D., 2005. Long term probability of detection of HIV-1 drug resistance after starting antiretroviral therapy in routine clinical practice. AIDS 19, 487-494.

Richman, D.D., Morton, S.C., Wrin, T., Hellmann, N., Berry, S., Shapiro, M.F., Bozzette, S.A., 2004. The prevalence of antiretroviral drug resistance in the United States. AIDS 18, 393-401.

Rosenberg, E.S., Altfeld, M., Poon, S.H., Phillips, M.N., Wilkes, B., Eldridge, R.L., Robbins, G.K., D'Aquila, R.D., Goulder, P.J.R., Walker, B.D., 2000. Immune control of HIV-1 after early treatment of acute infection. Nature 407, 523-526.

Rosenberg, E.S., Billingsley, J.M., Caliendo, A.M., Boswell, S.L., Sax, P.E., Kalams, S.A., Walker, B.D., 1997. Vigorous HIV-1-specific CD4+ T cell responses associated with control of viremia. Science 278, 1447-1450.

Ruiz, L., Martinez-Picado, J., Romeu, J., Paredes, R., Zayat, M.K., Marfil, S., Negredo, E., Sirera, G., Tural, C., Clotet, B., et al., 2000. Structured treatment interruption in chronically HIV-1 infected patients after long-term viral suppression. AIDS 1, 397-403.

Ruiz, L., Ribera, E., Bonjoch, A., Romeu, J., Martinez-Picado, J., Paredes, R., Diaz, M., Marfil, S., Negredo, E., Garcia-Prado, J., Tural, C., Sirera, G., Clotet, B., 2003. Role of structured treatment interruption before a 5-drug salvage antiretroviral regimen: the Retrogene Study. J. Infect. Dis. 188, 977-985.

Siliciano, J.D., Kajdas, J., Finzi, D., Quinn, T.C., Chadwick, K., Margolick, J.B., Kovacs, C., Gange, S.J., Siliciano, R.F., 2003. Long-term follow-up studies confirm the stability of the latent reservoir for HIV-1 in resting CD4+ T cells. Nat. Med. 9, 727-728.

Smith, K.Y., 2002. Selected metabolic and morphologic complications associated with highly active antiretroviral therapy. J. Infect. Dis. 185, S123-127.

Sterling, T.R., R.E. Chaisson, et al., 2003. Improved outcomes with earlier initiation of highly active antiretroviral therapy among human immunodeficiency virus-infected patients who achieve durable virologic suppression: longer follow-up of an observational cohort study. J. Infect. Dis. 188, 1659-1665.

Vogel, C.R., 2002. Computational Methods for Inverse Problems, Frontiers in Applied Mathematics FR23. SIAM, Philadelphia.

Walker, BD., Rosenberg, E.S., 2000. Containing HIV after infection. Nature Med. 6, 1094-1095.

Wein, L.M., Zenios, S.A., Nowak, M.A., 1997. Dynamic multidrug therapies for HIV: A control theroetic approach. J. Theor. Bio. 185, 14-29.

Wodarz, D., Arnaout, R.A., Nowak, M.A., Lifson, J.D., 2000. Transient antiretroviral treatment during acute simian immunodeficiency virus infection facilitates long-term control of the virus. Phil. Trans. Roy. Soc. Lon. B 355, 1021-1029.

Wood, E., Hogg, R.S., Yip, B., Harrigan, P.R., O'Shaughnessy, M.V., Montaner, J.S., 2003a. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4+ cell count is 0.200 to 0.350 x 10(9) cells/L. Ann. Intern. Med. 139, 810-816.

Wood, E., Hogg, R.S., Yip, B., Quercia, R., Harrigan, P.R., O'Shaughnessy, M.V., Montaner, J.S., 2003b. Higher baseline levels of plasma human immunodeficiency virus type 1 RNA are associated with increased mortality after initiation of triple-drug antiretroviral therapy. J. Infect. Dis. 188, 1421-1425.

Yeni, P.G., Hammer, S.M., Hirsch, M.S., Saag, M.S., Schechter, M., Carpenter, C.C., Fischl, M.A., Gatell, J.M., Gazzard, B.G., Jacobsen, D.M., Katzenstein, D.A.,

Montaner, J.S., Richman, D.D., Schooley, R.T., Thompson, M.A., Vella, S.,
Volberding, P.A.,, 2004. Treatment for adult HIV infection: 2004
recommendations of the International AIDS Society-USA Panel. JAMA 292,
251-265.