Graphical Abstract

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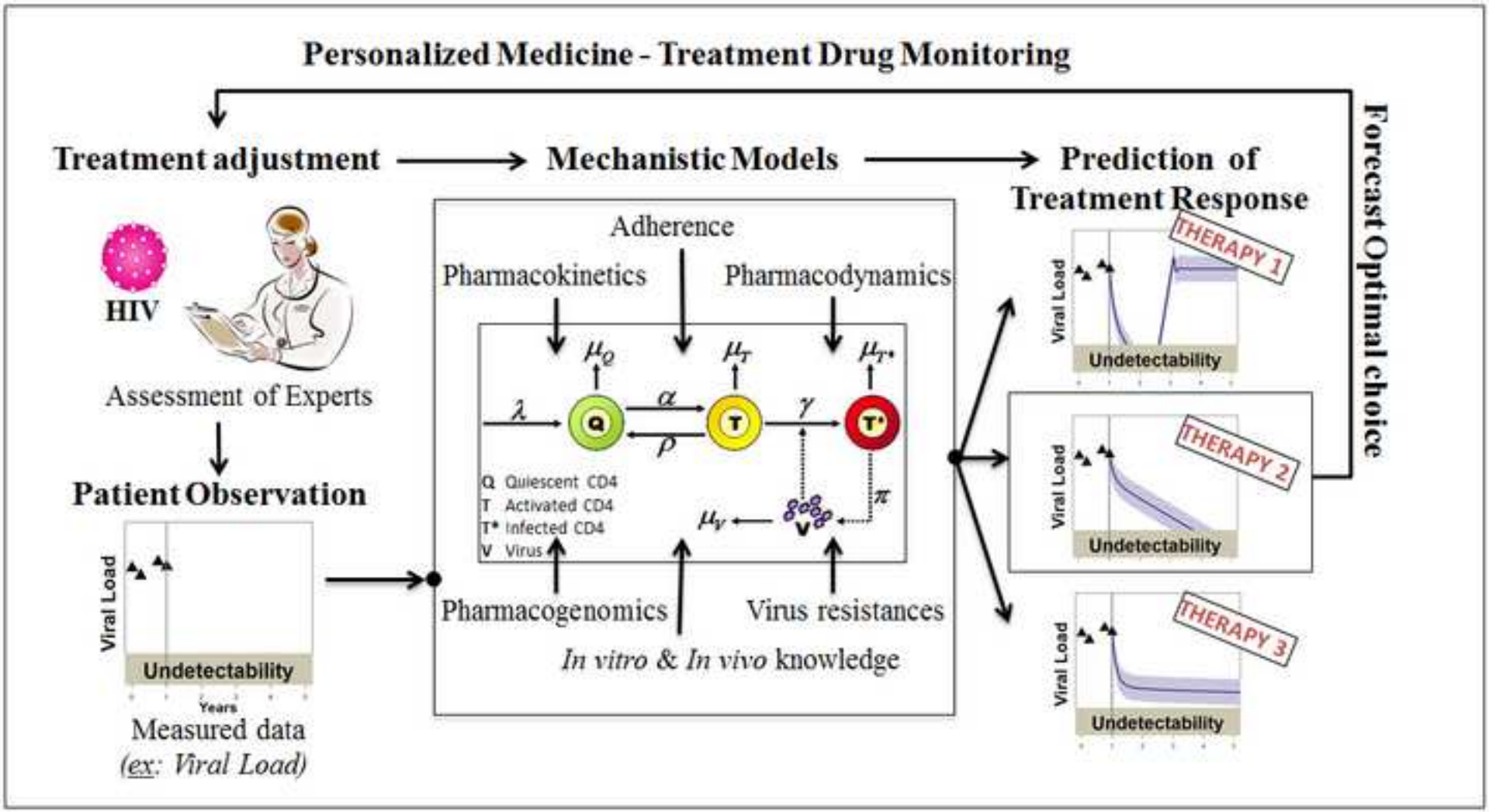

Dynamical models of biomarkers and clinical progression for personalized medicine: the HIV context

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Received 15 December 2012.

Abstract

Mechanistic models, based on ordinary differential equation systems, can show very good predictive capacities that will be useful to build treatment monitoring strategies. In this review, we present the potential and the limitations of such models for guiding treatment (monitoring and optimizing) in HIV-infected patients. In the context of antiretroviral therapy, several biological processes should be considered in addition to the interaction between the viral and the host immune systems: the mechanisms of action of the drugs, their pharmacokinetics and pharmacodynamics, as well as the viral and host characteristics. Another important aspect to take into account is clinical progression, although its implementation in such modelling approaches is not easy. Finally, the control theory and the use of intrinsic proprieties of mechanistic models make them very relevant for dynamic treatment adaptation. Their implementation would nevertheless require their evaluation through clinical trials.

Key words: **Mechanistic models, dynamic models, personalized medicine, HIV infection, biomarkers**

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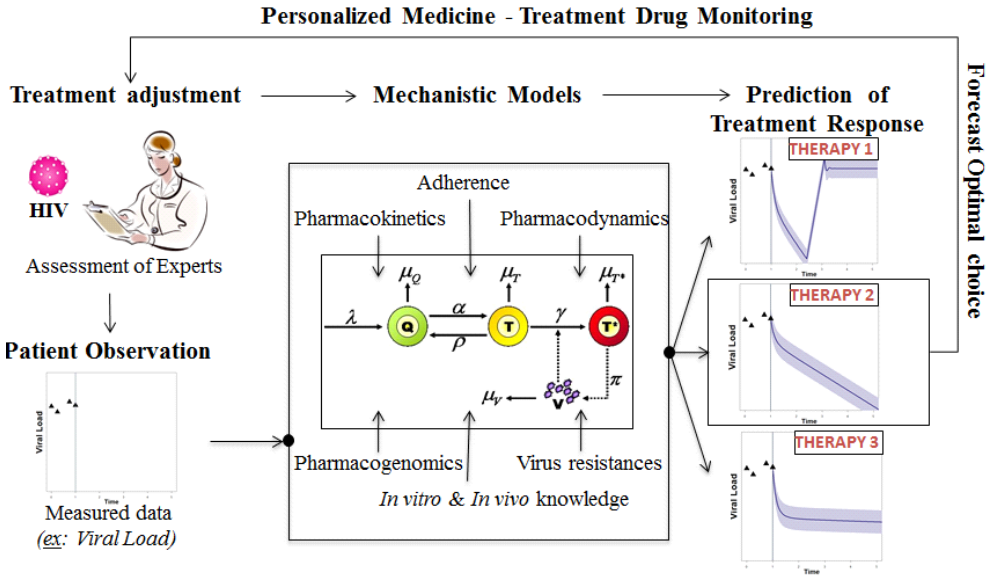
Abbreviations: Human Immunodeficiency Virus (HIV); Highly active antiretroviral Therapy (HAART); Therapeutic Drug monitoring (TDM); Structured Treatment Interruptions (STI); Ordinary Differential Equation (ODE); Pharmacokinetics (PK); Pharmacodynamics (PD); Pharmacogenomics (PG)

Graphical Abstract



1. Introduction

Guidelines for medical treatments are usually based on empirical results of clinical trials. For instance, for defining the treatment of an HIV infected subject, these recommendations pertain to four questions [1] : when to start antiretroviral therapy? What to start? When to change? What to change?

The guidelines are defined at a population level and are to be applied to all patients in a standardized way. Personalized medicine aims at defining more specific criteria for each patient. A usual approach is to define subgroups that would more likely benefit from starting or changing a treatment than others because of some individual characteristics based on clinical, biological or genetic markers. Once the treatment is started, another possibility is to observe the initial response of a given patient in order to adapt his/her treatment dynamically: this is often referred to as Treatment Drug Monitoring (TDM) or adaptive treatment strategy ([2]–[4]). Although mathematical models could be useful for this purpose, their use is actually limited by the complexity of their implementation. A well known example is the regulation of insulin injection based on glycaemia measurements [5]. In a model-based approach, the idea is to learn from the data collected from an individual to forecast the best choices likely to procure the best clinical outcomes. This relies on considering the patient as a "system" that is changing over time ([2], [6] and [7]). It then becomes possible to apply models to regulate this

system and thereby achieve more desirable outcomes based on control of the input and feedback [8].

The main objective of this review is to show how useful mechanistic models can be for personalized medicine, with a special emphasis on HIV infection. This is introduced in Section 2, where we also present a model of HIV dynamics which has already proven its predictive ability. In Section 3, we then review the potential of using additional information relating to the individual's clinical data related to the HIV infection such as patient's compliance, pharmacokinetics/dynamics data, viral and host genetics. In section 4 we discuss attempts that have been made for treatment monitoring and the challenges that remain to be addressed.

2. Models for HIV biomarker dynamics and their predictive ability.

2.1. A tool: the dynamical/mechanistic models

In medicine and especially in clinical research, mathematical models can be useful for dealing with the growing amount of information. More and more factors are recorded for each patient, and more and more biomarkers are measured repeatedly over time. The aim of modelling is usually to summarise multi-dimensional datasets, as well as trying to predict outcomes in future patients. A summary may be a set of independent factors associated to the occurrence of a disease, such as in traditional epidemiological studies. Regarding models, two types can be distinguished, i.e. 'descriptive' and 'mechanistic' models. Descriptive models are designed using a standard structure that will best fit all available data, with a view to capture association between factors and the evolution of the disease. For instance, if a continuous marker is repeatedly measured over time and has a non-linear evolution, a model based on non-linear mixed effect could then be used. Once the estimates have been obtained, the interpretation of the results might then lead to biological hypotheses explaining the link between factors and the change in the marker. In contrast, the "mechanistic" approach starts from biological knowledge. Biological knowledge is translated into a set of mathematical equations, generally a system of differential equations. Here, we will restrict our discussion to the case of ordinary differential equations (ODE), although models have also been based on the more complex partial differential equations or stochastic differential equations. The ODE system defines a dynamical system for which the behaviour can be studied. There generally are, however, several unknown parameters involved in such a system of differential equations,

and its behaviour will of course depend on the value of all parameters, including the unknown ones.

Mechanistic models based on differential equations are commonly used in physics. Using this type of models in biology is challenging because the biological mechanisms are different from physical laws and the biological systems are generally more complex than physical systems. In other words, models are always a simplification of reality, but an acceptable simplification is often more difficult to achieve in biology than in physics. The gap between model and reality may be reduced by increasing the model's complexity, or by introducing stochasticity [9]. Moreover, in physics many parameters are assumed to be known while in biological models, nearly all the parameters are either estimated, or unknown. Thus, the issue of parameter estimation, which is a statistical issue, is a major challenge in biological models. As a consequence, in order to be able to estimate the parameters, a compromise has to be found to design a reasonably simple model which correctly fits the observed data, an issue coined in statistics as the parsimony principle. In mechanistic models we have the additional requirement that the structure of the model must represent important characteristics of the underlying biological mechanisms.

Using a mechanistic model presents the advantage of bringing external information to the analysis, i.e. information coming from the knowledge of the biological mechanisms at work, which may lead to a comparison of models reflecting different biological mechanisms [10]. Interaction between various biomarkers may be better captured by the mechanistic modelling than by a complex descriptive model. For instance, several descriptive models were suggested for jointly modelling two markers in HIV infection such as viral load and lymphocytes T $CD4^+$ count ([11]–[14]). However, none were fully satisfactory because none gave both a good fit of the data and an easy biological interpretation of the parameters.

The mechanistic nature of the model should ensure two fundamental properties: i) the parameters should be universal (at least approximately) in the sense that their value should be consistent across any datasets (e.g. cell survival rate); ii) the predictive ability should be better than that of a descriptive model, that is in situations with data different from those used for learning the model. Once a model has been obtained and shown to have a good predictive ability, it becomes possible to envisage using it for controlling the response, for example for adapting and monitoring drug treatments.

2.2.An example of field of application: HIV infection

The HIV infection provides a good example of the use of mathematical mechanistic modelling. The basic biological knowledge is as follows. The HIV virus uses the CD4 receptor to enter into a cell that it will infect: thus the target cells are those presenting a large number of CD4 receptors, essentially the $CD4^+$ T lymphocytes. It is the use of mechanistic models that helped to reveal that a high turn-over of virus and cells is a fundamental phenomenon in the HIV disease [21].

When infected subjects are given a potent antiretroviral drug, the viral load decreases sharply. Assuming there is no more viral replication, the half-life of the virus can be estimated by fitting a simple exponential model (which is the solution of the differential equation $\frac{dV}{dt} = -\mu_V V$, where μ_V is the viral load). Further refinements provided updated estimations of the infected cells half-life [15]. This revealed that the half-life of the virus was short [16]. Hence, the equilibrium state observed during the asymptomatic phase of the HIV disease was actually associated to a constant renewing of both the virus and target cells with a very high turnover rate. One implication of these results was the very high probability of mutations of the virus in just one day. This understanding constituted one of the bases for the rationale of combined antiretroviral therapies that is now the standard of care. These models, as any model, made several strong assumptions, including a perfect efficacy of the antiretroviral treatment (see [17], [18] for a review). This assumption was acceptable as a first approximation because the antiretroviral treatments were highly potent on a short term. However, researchers have also used these models to estimate the antiviral potency of the antiretroviral regimen [19]. Although this objective is clinically highly relevant, several methodological issues arise when embarking in such studies. This is presented in part in the Wu's paper of the present issue (see [20] in this journal) and summarized in the following paragraphs.

A wide variety of models exists. As mentioned above, in the pioneering work of Wei et al. [16], only the viral decay was modelled. A model that also incorporated viral production with separate analysis of the viral load and CD4 count was then developed [21]. Later, many proposals were made by various authors, leading to models including more compartments. First, distinguishing between uninfected and infected CD4+ T lymphocytes (in short "CD4") led to detect that there are heterogeneous half-lives for infected cells and that more complex nonlinear models are needed to accurately describe long-term viral decay ([15], [22]). Several other models were then proposed, assuming exponential life-span of infected CD4 [23], different maturation stages of CD4, CD8 modelling [24] and mutations, most of the time

modelled by a finite number of mutants in a discrete form ([25]–[27]). Most of these models were associated to new breakthroughs in the understanding of the infection, and were designed to include the action of antiretroviral drugs. The effects of different drug classes, however, have typically been aggregated in these modelling approaches, with some notable exceptions ([19], [28]–[30]).

Nevertheless, most of these works are burdened by problems of identifiability: see [31], [32] for a description of this issue in the HIV setting. One of the main problems is that, while it is useful to distinguish several types of cells, leading to several compartments, only very few compartments can be observed clinically (typically two in the HIV setting: CD4 count and viral load). Because of the difficulty of estimating parameters, most authors used mathematical modelling as a tool for studying possible dynamics of the system when all the parameters are fixed in advance. With carefully chosen values of parameters, this type of approach can indeed be valuable, for example to examine hypotheses on different biological mechanisms [33], to perform simulations of mutations occurrence [34], to compare designs of therapies ([30], [35]). In a particularly interesting instance, Smith and Wahl proposed an impulsive differential equations model accounting for kinetics of drug actions to evaluate the effect of the duration of the interval between administrations [30]. It was found that a high frequency and a short interval dosing interval is compulsory to maintain a "normal" T cell count and a threshold defined per individual can result in optimized dosing intervals. However the behaviour of dynamical systems strongly depends on the values of the parameters. This type of approach is thus limited to an exploratory phase.

We believe that the strength of the mechanistic models approach for medicine individualization can be exploited only if the parameters have been estimated from data. Estimation is a statistical problem, and this represents a particularly challenging one for mechanistic models. A proposed solution to the problems related to identifiability, is to fit the model not on a single patient but using a sample of patients. However, the assumption that the parameters are the same for all patients does not hold. Treating some parameters as random allows taking into account inter-patient variability. Statistical approaches using random effect models have been developed and applied to data from large clinical trials samples. One should note, however, that fitting ODE-based models with random effects is numerically challenging (see [36] for a review and [37]–[41] among others for original developments).

2.3. Predictive ability of the "activated cell" model in HIV infection

In this section, we illustrate the good predictive ability that can be achieved with a particular mathematical model applied to a HIV clinical trial. We used the data of the controlled randomized open-label ALBI ANRS 070 trial [42] in which three antiretroviral strategies based on two nucleosidic reverse transcriptase inhibitors (NRTI) were compared in 151 previously untreated patients over 24 weeks. The 51 patients from arm 1 received the d4T (stavudine) + ddI (didanosine) treatment, with drug doses adjusted to their weight: d4T 250mg plus ddI 60mg for patients under 60 kg, and d4T 400mg plus ddI 80mg for those above 60kg. For arm 2, 51 patients received 500mg of zidovudine (AZT) and 300mg of lamivudine (3TC). In the third arm (49 patients), patients were given the same treatment as in arm 1 (D4T+ddI) for 12 weeks and then switched to the treatment given to arm 2 patients (AZT+3TC) for the remaining 12 weeks. CD4 counts and viral loads were measured every 4 weeks until 24 weeks. Two patients dropped out before the time of the first blood sample collection, so 149 patients were available for the Intent-To-Treat analysis (ITT). For each patient, changes in dose were either self-reported or declared by the clinician. The details of the design and the collecting methods have been described in details elsewhere [42].

The ''activated cell'' model is represented by a four-dimensional ODE system, featuring quiescent (Q) and activated (T) uninfected CD4+ T cells, infected CD4+ T cells (T*) and viruses (V) concentrations (see Figure 1 and **Error! Reference source not found.** for parameters description):

$$\begin{cases} \dfrac{dQ}{dt} = \lambda + \rho T - \alpha Q - \mu_Q Q, \\ \dfrac{dT}{dt} = \alpha Q - \gamma V T - \rho T - \mu_T Q, \\ \dfrac{dT^*}{dt} = \gamma V T - \mu_{T^*} T^*, \\ \dfrac{dV}{dt} = \pi T^* - \mu_V V. \end{cases}$$

To take inter-patient variability into account, parameters can be modelled as the sum of a population (fixed) parameter $\tilde{\theta}_0$ and a random effect b_i having independent standard normal distributions: $\tilde{\theta}_i = \tilde{\theta}_0 + b_i$ leading to a mixed effects model. After a forward selection strategy [43], parameters $\tilde{\alpha}$, $\tilde{\lambda}$ and $\tilde{\mu}_{T^*}$ were found to vary substantially among patients and were selected for having random effects, while the other parameters were assumed constant in the

population. Because the antiretroviral drugs considered were inhibitors of the reverse transcriptase, the treatment was assumed to act on the infectivity parameter γ [44]. For a specific treatment, the standardized dose d (smoothed over three times, 100% if full-dose, the percentage of the drug intake otherwise) was introduced as covariate with a power function κ and infectivity depended on treatment effects β as follows: $\tilde{\gamma}_i = \tilde{\gamma}_0 + \beta d^{\kappa}$. This can be easily extended to treatment regimens by considering as many treatment effects and power functions as the number of drugs in combination.

Although the model distinguishes between quiescent, non-infected and infected CD4, only the total number of CD4 is observed. We built an observational model for the $\log_{10}$ of the viral load and the fourth root of total CD4 count (written Y = [log10(V), (Q+T+T*)0.25]) plus a measurement error that we assumed Gaussian with standard deviation. A method for parameters estimation based on penalized maximum likelihood can be found in [39] and it has been implemented in the NIMROD program (Normal approximation Inference in Models with Random effects based on Ordinary Differential equations) which is available for download [45]. The penalized likelihood approach can be thought of as an approximate Bayesian approach: the approximation consists in approximating the posterior distribution of the parameter by a normal distribution (which is asymptotically justified). Other software programs are available for fitting such models [46].

From the ALBI data, we constructed a training dataset for estimating the model parameters and a validation dataset on which we performed predictions. To avoid over-fitting, we excluded the patients for whom we made predictions from the learning set. A description of the analysis can be found in [47]. The individual predicted trajectories of viral load and CD4 count were computed by plugging individual estimates of parameters into the ODE model and by computing the solutions numerically.

We assessed two endpoints: prediction of treatment changes and dose changes. In the third arm of ALBI, patients switched treatment after 12 weeks. To examine whether it was possible to forecast their response to the new treatment given during the remaining 12 weeks, we selected patients at each decile of the distribution of HIV viral load at the end of the study and excluded them from the learning dataset. For each patient belonging to these different deciles, we used the first 12 weeks associated with the first 4 measurements to compute individual parameters and predict the patient's response to the treatment modification. Figure 2 presents the individual prediction of the markers for a patient (the median patient for viral load) who

switched from d4t+ddI to AZT+3TC. The predictions thus obtained were quite good: only 4.9% of the observations were out of the 95% measurement error predictive intervals. This high quality of prediction suggests that this arm could actually have theoretically been avoided since we were able to predict the marker dynamics reliably for each individual. The same type of analysis was performed to assess the predictive abilities of our models to dose changes. In spite of a rough function linking the dose and the effect, predictions of the response to treatment changes were also found to be quite good (
Figure 3 and Figure 4a). Taken together, Figure 4a and Figure 4b illustrate that, as expected, these predictions are better if many observations from the patients are used to build the predictions. In other words, short-term predictions are better than long-term predictions. In this particular example, CD4 counts can be correctly predicted using three patients' observations of biomarkers (both viral load and CD4 count), whereas one is not sufficient.

It should be recognized that the quality of these predictions is also linked to the most likely hypothesis that the AZT+3TC regimen has a lower potency in this trial. Indeed, the prescribed AZT dose of 300mg/d was probably too low if we consider that the current dose prescribed nowadays is 600mg/d. Albeit, additional virus genotype data did not allow to conclude for a higher incidence of resistance mutations in AZT+3TC group [48].

In conclusion, the individual predictions of the mechanistic model in this trial were found to be very good, thanks to the relevance of the model used in this application and a full estimation of all the parameters jointly. If the mechanistic model does not include a biological mechanism playing an important role in a given circumstance, however, the predictions will probably not be as good as those we observed in the ALBI trial. Further work is currently ongoing to look at the robustness of such models with more up to date antiretroviral therapies. Moreover, since it is generally accepted that this kind of model is by definition miss-specified, other components will have to be considered to go further.

3. Including in vivo/in vitro drug efficacy and compliance

3.1. The type of drug mechanism

A potential power of mechanistic models is to distinguish between the mechanisms of action of different antiretroviral agents. Nowadays, five classes of antiretroviral agents exist which do not act on the same pathways (see [49] for a review). Entry inhibitors, interfere with the binding, fusion and entry of the HIV virus. Reverse transcriptase inhibitors (RTIs) impair the synthesis of the HIV DNA genome from the RNA strands. In mechanistic models, we may

consider that drugs belonging to these two classes decrease the rate of infection of the CD4. Consequently, infectivity parameter (γ) or analogue should be reduced. Integrase inhibitors block the action of the integrase, a viral enzyme that inserts the viral genome into the cell nucleus. Different stages of infection of the CD4 cells can be modelled, the last stage being virus production. Thus, integrase inhibitors diminish the rate of conversion from early stage infection to late-stage infection. It has been argued that the steep viral load decrease observed with integrase inhibitors is due to the action of the drug at a rather late stage of the viral life cycle [29]. Finally, Protease Inhibitors (PIs) prevent the viral replication by inhibiting the activity of proteases enzymes used by the virus to cleave nascent proteins for the final assembly of new virions. This can be represented in the model by assuming that part of the produced viruses are defective and non-infectious [50]. Altogether, antiretroviral drugs do not act at the same stage of the viral life cycle; this has a significant impact on the dynamics of the system and must be adequately represented in the models developed. Of note, the ability to distinguish the biological mechanism of any antiretroviral drug will depend on the precision of the measurement (e.g. infected cell, integrated DNA…). In this regard, the models used in most previously published studies have assumed known and/or constant effects of the drugs ([50]–[52]).

3.2. Pharmacokinetics

Pharmacokinetics (PK) of antiretroviral drugs are also important factors, but they are difficult to use directly because of the high variability between subjects in the drugs' absorption, distribution, metabolism and excretion [53]. Moreover, bioavailability and protein binding can complicate the drugs' quantification *in vitro* and cause confusions [54]. Although the antiretroviral activity should be linked with plasma concentration (PK), this is only ever a correlation with the drugs' intracellular concentrations, which are the truly significant variable [55]; this is mainly because antiretroviral agents act mostly at intracellular sites. Quantification techniques thus need to improve before PK values can be used reliably to evaluate treatment efficacy and clinical endpoints. Thus, the PK data may be insufficient to guide the adjustment of administered doses in patients appropriately and must be combined with considerations about pharmacodynamics (PD).

Several factors are important to determine PK-PD relations, ranging from inter-patients differences to heterogeneity of viral responses to drugs, as well as interactions between the

two. **Error! Reference source not found.** presents a summary of some of the most used indicators. Most of the time, PD is evaluated *in vitro* since it is easier to measure viral replication in the presence of various concentrations of the drug. The most commonly used indicator is the IC50, defined as the concentration of drug required to achieve 50% inhibition for a specific strain of virus. This is a static indicator that does not indicate what the impact of lower or higher drug concentrations would be. Moreover, it is a poor reflection of antiviral activity since it depends on the intrinsic properties of the drug, the kinetics of the stage of the viral life cycle and the kinetics of the infected cells [17]. Inhibitory Quotients (IQ*s*) are associated with the virological response since they are defined as the ratio between drug concentration (C_{through}, plasma concentration before the next dose) and IC50 [56]. IQs are, however, also constant factors and do not describe dynamic variations according to the administrated doses. Hence, using dose-response curves from infectivity assays has been suggested for quantifying the antiretroviral potency [57]. The Instantaneous Inhibitory Potential (IIP) is a function of the dose (D). It is dynamic thanks to the Hill coefficient (m) that is the slope of the dose-response curve. This is particularly interesting because it allows to use the number of infected cells as a direct readout for viral replication. In practical terms, IIP is the logarithm of the number of single-round infection events reduced by a drug [58]:

$$\mathrm{IIP}(D) = \log_{10}\left(1 + \left(\frac{D}{\mathrm{IC50}}\right)^{m}\right)$$

Thus, the effectiveness of an antiretroviral *in vivo* is determined by m and IC50. It then becomes possible to introduce time variations by using the PK for a particular dosing schedule leading to $D(t)$ (where t is the time). This time-varying ratio between the dose and IC50 in IIP has an interpretation comparable to IQs [58]. Moreover, apart from the dynamical advantages, IIPs are similar to IQs for predicting HIV responses to antiretroviral agents [59]. Furthermore, IIPs are sensitive to PK-boosting effects and interactions between drugs [60]. Empirically observed interactions of antiretroviral drugs in clinical trials are reviewed in [61]. There is no metric to describe the combined effect of multiple drugs, but, four categories of interactions can be distinguished: synergism when one drug enhances the effect of the other; Bliss independence when each drug inhibits a portion of the targets; Loewe additivity that assumes that two inhibitors act on a target through a similar mechanism; and antagonism when action of a drug inhibit the action of the other [62]. Combined IIP can be evaluated *in vitro* and reflects these interactions. An exhaustive listing for more than 166 pair-wise and 1892 three-ways combinations over 20 treatments is available in [63]. This provides a large

dataset of *in vitro* potency assessment and a quantitative basis to compare and analyse treatment effects.

However, extrapolating from *in vitro* data to *in vivo* situations is complex. First, *in vitro* susceptibility assays do not follow the viral dynamics during days or weeks but at a specific time point in specific conditions [64]. Second, variations of several fold of these PK-PD indicators can occur during particular clinical situations such as acute infections, advanced HIV disease or pregnancy [65]. This can, however, be partially corrected by introducing explanatory variables, or by introducing a conversion parameter that has to be estimated from the data [66]. This is analogous to introducing a scaling factor that is reflective of the uncertainty between the drug measurements of drug potency *in vitro* and the specific model-based drug potency *in vivo* [67] .

3.3. Compliance

Compliance to treatment is essential for achieving efficient concentration at the target tissues. Lack of compliance can be represented by dose-delay or dose-omission. Although many methods exist, adherence remains very difficult to assess [68]. Poor compliance is a key factor for explaining viral load variations and is strongly associated with treatment failure ([69], [70]) as it favours viral mutations and therefore viral resistance to treatment (see next section). Nevertheless, the impact of compliance varies according to the type of antiretroviral regimen [71]. For estimation concerns, poor or unmeasured compliance can result in an underestimation of drug effectiveness leading to overestimation of drug dosage [72]. A classical and convenient way to take compliance into account in models is to include a compliance rate $A(t)$ and to replace the dose $D(t)$ by the product $A(t)D(t)$ in the PD model ([38] and [73]–[77]).

3.4. Viral mutations

Genotypic and phenotypic characteristics of the virus can also greatly influence the response to antiretroviral treatment. Genetic barrier for resistance refers to the number of nucleotide changes a virus needs to accumulate to become resistant to a given antiretroviral drug. Information on patterns of resistances and cross-resistances is important for making decisions on how to change and combine drugs to achieve an optimum antiviral effect. Hence, genotype

information is increasingly used for deciding which antiretroviral drugs should be included in a given regimen.

Genotypic and phenotypic assays based either on the detection of specific point mutations or on complete DNA sequencing are increasingly available [78]. *In vitro* assessment of HIV fitness has been extensively studied by different techniques; see [79] for a complete review of this topic. In short, resistance is typically measured by the virtual phenotype which is the fold change in IC50 relative to the Wild-Type (WT) virus ([80], [81]). A derivation of this is the virtual Inhibitory Quotient (vIQ), which is the IQ divided by the virtual phenotype and has been shown to have a significant link with the viral response to treatment [82]. An improvement is to introduce vIQs in IIPs (described in Section 2.1 multiplying the IC50 by the virtual phenotype leading to virtual IIPs) because this allows accounting for the steepness of the dose-response curves (represented by Hill coefficient *m*). This is particularly important for PIs whose IC50 is usually the same in mutant variants and WT but for which a higher dose is needed to achieve viral extinction because *m* is smaller [83]. *In vivo*, the viral response to a new antiretroviral regimen is studied according to the genotype measured at the time of treatment change. Various approaches have been proposed to predict the response to antiretroviral regimen according to the baseline genotype [84].

In mathematical modelling, mutations are introduced by adding virus compartments to account for different strains of virus (for an example, see the pioneering work of Nowak et al. [85]). One approach consists in considering that several genotypes of the virus, $V = (V_1 \dots V_K)$ exist in each patient. They are called quasi-species. The different genotypes may have different fitness, which is efficiency of replication. In real life, the number of genotypes can be large, but numerical complexity limits the number of possible genotypes that can be represented in a model [86]. Another approach which is easier to build focuses on vIIPs instead of IIPs, and modulates the treatment effect depending on the mutant variant k. ODE-based models with immune cells and multiple strains of viruses have allowed the comparison of scenarios; as an example of results, it has been calculated that the probability that resistant mutants pre-exist to treatment is higher than the probability that resistant mutants are generated during therapy [87]. In similar models, Rong et al. introduced the effects of compliance to short-term [77] and long-term [88] treatment, and showed that many variants of the virus live as quasi-species in the host. Mutant variants that are selected have a lower sensitivity to the antiretroviral drugs and are associated with a rebound of the viral load [89]. The resistant viruses are capable of replicating better than the sensitive viruses and will

therefore be positively selected [90]. The viral fitness of a mutant is, however, generally lower than that of a wild type; consequently, replication, virulence, and transmission of the selected mutant viruses may be reduced compared with those of the wild-type [91]. Specific models have been suggested for estimating these differences in viral fitness ([92], [93]).

An integrated model has been recently proposed by Rosenbloom et al. [76]. The authors suggested that this type of approach might be more relevant for the evaluation of the likelihood of reaching a good antiviral response than the use of a genotype because this latter information is based on meta-analysis of data obtained from various regimens in patients with various characteristics. However, the effect of mutations is probably highly dependent on this context according to the results. In practice the detection of resistant mutants is commonly used to choose or modify the drug regimen given to a patient but this kind of knowledge has not yet been incorporated in a mechanistic model for personalized medicine.

3.5. Host Genetics

It is not common to use pharmacogenomic (PG), that is the patients' genetic data, for determining the choice of antiretroviral drug but this may be relevant in some very specific indications. For instance, the HLA-B*5701 allele has been shown to lead to a risk of about 50% of hypersensitivity with abacavir, making the screening of this haplotype systematic before prescribing this drug [94]. Drug-drug interactions and genetic polymorphism in drug-metabolizing enzymes and drug transporters (MDR1, CYP3A5, CYP2C19…) contribute to wide variability in drug pharmacokinetics, response to therapy and toxicity ([95]–[98]). For instance, using a population pharmacokinetics model including genetic characteristics, several CYP2B6 polymorphisms have been identified as being associated with steady-state nevirapine clearance among HIV-infected patients [99]. A dynamic approach is valuable to model gene interaction in a quantitative manner [100]. A modelling strategy with linear ODEs has been proposed by Lu et al. to capture gene regulatory network [101]. The perspective to introduce biomarkers and antiretroviral drugs as new compartments in these systems is appealing and can bridge the gap to combine PK-PD-PG to explain HIV dynamics under treatment. To date, however, the information on individual susceptibility to antiretroviral drugs remains sparse [96]. The inclusion of any PG data in mechanistic models, provided that the information is available, can be expressed by modelling some parameters as a function of individual values. The remaining inter-individual variability is then taken into account through random effects on parameters, especially those representing treatment effects.

Including PG information would decrease the unexplained variability captured by the variance of the random effect.

3.6. Including clinical progression

The first outcome of interest when modelling the response to antiretroviral treatment is the viral rebound [76] followed by the CD4 dynamics since both these markers are very good prognostic markers ([102], [103]). These markers, however, are still imperfect surrogate markers of clinical outcome, that is, it is not possible to predict the exact clinical effect of an antiretroviral treatment by just observing an increase in CD4 or a decrease of HIV viral load ([104], [105]). This is even more the case nowadays because AIDS-classifying diseases are less common, whereas the proportion of deaths due to cardiovascular diseases and cancer is growing [106]. Also, depending on the type of therapeutic approach used, the ability of these markers to reflect the clinical benefit is not guaranteed. For instance, the administration of the IL-2 cytokine results in a substantial increase of CD4 but without any significant clinical benefit [107].

Therefore, it may be important to model the dynamics of biomarkers and clinical progression jointly. Many joint models have been proposed in the literature, including applications in the HIV-AIDS field ([13], [14] and [108]–[111]). Wu et al. [112] proposed a joint model including a non-linear (bi-exponential) mixed effect model for the viral dynamics with a proportional hazards model for the time-to-disease progression, and a complete mechanistic model based on ODE including a time-to-event process has subsequently been proposed by Guedj et al. [113]. Starting from a previous ODE-based model [39], the time-to-disease progression has been linked to the marker's predictions at any time by a proportional hazard model. Such joint models of longitudinal markers and time-to-event processes take into account the informative missing data process due to the censoring of observations after the occurrence of disease progression. Furthermore, an easier two steps approach, where the longitudinal model is fitted first and predictions are then used in a survival model, ignores the variability of the parameters of the longitudinal model estimated in the first step [109]. Finally, in the context of adaptive treatment, one needs dynamical models from which predictions are available at any time, thus requiring joint models.

What is interesting with such models is that one can obtain predictions of changes in markers (CD4 count, viral load) but also the probability of disease progression (according to the change in markers). A treatment monitoring based on this type of models sounds very useful.

However, the wide spectrum of clinical diseases observed today in HIV-infected patients is due to various processes, from antiretroviral side effects [114] to the consequences of long-term HIV infection (cell activation, inflammation) [115]. Therefore, including all types of clinical events may result in a highly complex model. On the other hand, this type of model could be devoted to specific questions. For instance, with the objective of finding an optimal dose of antiretroviral, a model that includes the effect on the viral dynamics as well as the probability of side effects could serve at finding a good compromise between viral efficacy and side effects.

4. Toward the use of mechanistic models for personalized medicine

4.1. Treatment monitoring using mechanistic models

HAART succeeds in reducing viral load in most HIV infected patients but does not eradicate the virus. Thus the treatment has to be taken life-long. To reduce the burden of side effects it has been proposed to interrupt the treatment under certain conditions or to find an optimal dose. Structured Treatment Interruptions (STI), where antiretroviral treatments are stopped either during a given period or according to CD4 counts has been a first attempt to optimize drug administration ([28], [116] and [117]). These periods of treatment interruption were supposed to boost the immune system, to offer pill burden vacancy and decrease side effects. Some studies have also evaluated strategies where the immune system was boosted with vaccine and/or interleukin (IL2) before interruption ([118], [119]). Unfortunately, the evaluation of the effect of STI on clinical outcomes through randomized clinical trials have concluded that STI were harmful [120]. Control theory (taken from engineering literature) has been suggested to find the optimal interventions that reduce a given cost function [121]. Quadratic cost functions that weighted system response (viral load or CD4 count)) and side-effects of the drug have been proposed [9]. Although conceptually interesting, this approach is not realistic because i) the model is not known, ii) the choice of the cost function is debatable, iii) the treatment cannot be continuously adapted. More recent approaches tend to get free from cost functions [122] and do not aim at adapting the dose continuously [123]. Prague et al. [47] proposed to give the lowest dose for which there is infection control. This is based on ODE stability criterion, the reproductive number R_0 also used in SIR models: if $R_0 < 1$ there is extinction of the infection. Thus the idea is to give the lowest possible dose that ensures $R_0 < 1$. Such an approach was applied to the ALBI clinical trial. The patients in the most potent group (d4T+ddI) were selected to evaluate the best dose change required. A specific patient with

undetectable viral load (below 50 copies/mL) during all the study after treatment initiation was proposed a dose reduction up to 53% of his initial dose whereas another patient with default in infection control during antiretroviral therapy was assigned a moderate dose increase. Then, if we observe how the patient reacts to the new dose it should be possible to update it in an iterative manner. In Figure 5, this kind of adaptive treatment strategy is illustrated by a feedback loop where patients go iteratively through two steps: observation then adaptation of their treatment. Such recommendations should be tested in order to be validated and in order to observe how patients react.

4.2. Implementing the TDM in clinical settings

Before the efficiency of TDM on HIV disease control can be tested, a first step should be to assess the capacity of TDM to influence the concentrations of drugs or biomarkers values into a predefined range so as to validate or invalidate the model used, and the TDM approach. This could initially be applied to all antiviral drugs, with a view to focus subsequently on more "targetable" drugs. This was already done by Duval et al. [124], who showed that, among PIs, dose TDM is more likely to be useful for indinavir and lopinavir than for nelfinavir. Variability should also exist between treatment regimens: on this subject, Back et al. argue in favour of TDM for PIs instead of NRTIs [125].

It is still difficult to build an acceptable design to test TDM. To date, TDM trials are complex to interpret and statistically underpowered [126]. The method of choice would be a randomized clinical trial comparing at least two strategies: standard of care (SOC) and TDM. A flow chart, Figure 5, describes the general design. Primary and secondary end-points will have to be carefully chosen with a good metric to assess TDM success or failure. Moreover, three outcomes are to be assessed: safety, efficacy and cost-effectiveness. Concerning safety toxicity and tolerability, the trial must include intermediate analyses so as to stop the trial in case of harmful results, see STI trials as an example [120]. Evaluation of efficacy regarding impact on viral load and CD4 count is not sufficient, to assess long-term validity of the TDM we see as compulsory to evaluate the emergence of viral mutation and recommend a long-follow-up of patients after stopping the treatment adaptation strategies. Finally, cost-effectiveness should be considered in case of superiority proof of TDM against SOC because the higher frequency of biological observations and medical visits is to put in perspective with a substantial benefit of TDM.

It exists illustrations of the design we presented: one of the simplest treatment adaptations in HIV infection is based on the use of viral resistance information. Several randomized clinical

trials have been performed to evaluate a strategy based on resistance information compared to standard of care ([127]–[129]). Specific designs could, however, be considered for the evaluation of more complex approaches for dynamic treatment. Murphy [130] advocated for the use of adaptive design, where the term "adaptive" refers to the experimental design that could be flexible: changing strategy allocation according to the responses in previous patients. An example of this, he proposed is the sequential multiple assignment randomized (SMAR) trials where each individual may be randomized multiple times and multiple randomizations occur sequentially through time.

Finally, an easily acceptable way of testing, which can be adapted retrospectively by adjusting on confounders, should be to analyse a previously designed clinical trial in two groups: after the forecast of the best treatment according to mechanistic models, comparing results between patients who had treatments below TDM targets and others. This kind of comparison was partly used by Best et al. [131] to assess antiviral drug dose TDM and this study showed that patients below TDM forecast tended toward a greater viral load.

5. The challenge of the approach

In this paper, we have shown that, in HIV patients, mechanistic models could be very useful to perform individual prediction of the response to an intervention based on antiretroviral drugs and could therefore be a useful tool for treatment monitoring. This could also be the case for other interventions such as immune based therapy ([119], [132]). However, the mechanistic model needs to i) include relevant biological processes involved in the response ii) to be fed enough data (that is with relevant markers measured repeatedly). In some circumstances such as in the ALBI trial this could be achieved, but more developments are probably needed to cope with the numerous types of drugs available today. The implementation of processes such as the occurrence of genotypic mutation or the effect of known host genotype on the treatment efficacy could be achieved without too much complexity. In such cases, however, the restriction might come from the absence of measured information. Also, in line with the parsimony principle that maximizes the external validity of the predictions, simple models should be prioritized. Then, if a good model proves relevant for current treatments, the next step would be to evaluate the potential of such approaches for treatment monitoring by well-designed clinical trials.

6. Acknowledgements

We thank the Vaccine Research Institute for providing grant support and Carol Featherstone for the editing of the English.

7. References

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8. Tables and figures

Figure 1 - Graphical representation of the "Activated cells model"

Figure 2 - Viral load (log10 copies/ml) and CD4 count (cells/L) predictions for patients at median of the final HIV viral load distribution for patients in ALBI switch arm (#642). Triangles are observations, Red Diamonds are observations outside the CI; Black lines are fits, blue line on the left of the horizontal line is prediction. Shaded zone represents the 95% measurement error predictive interval. Horizontal dashed line represent left censoring threshold for viral load. Bottom part of graphs gives treatment posology.

Figure 3 - Viral load (log10 copies/ml) and CD4 count (cells/L) predictions for patients at quartiles (Q1 and median) of the final HIV viral load distribution for patients in ALBI experiencing dose changes. Triangles are observations, Red Diamonds are observations outside the CI; Black lines are fits, blue line on the left of the horizontal line is prediction. Shaded zone represents the 95% measurement error predictive interval. Horizontal dashed line represent left censoring threshold for viral load. Bottom part of graphs gives treatment posology.

Figure 4 - Viral load (log10 copies/ml) and CD4 count (cells/L) predictions for patient at third quartile (Q3) of the final HIV viral load distribution for patients in ALBI experiencing dose changes. Triangles are observations, Red Diamonds are observations outside the CI; Black lines are fits, blue line on the left of the horizontal line is prediction. Shaded zone represents the 95% measurement error predictive interval. Horizontal dashed line represent left censoring threshold for viral load. Bottom part of graphs gives treatment posology. Two graphs at the lower part of the figure represent predictions for the same patient (Q3) demanding on the number of observations used to construct predictions. Left is on a long-term (1 observation used to predict a 6 points trajectory) and on a short term (3 observations used to predict a 3 points trajectory).

(a) Only the baseline observation is used to build long-term predictions.

(b) First three observations are used to build shorter-term predictions.

Figure 5 - Flow chart of a standard clinical trial testing TDM against SOC.

Figure 1
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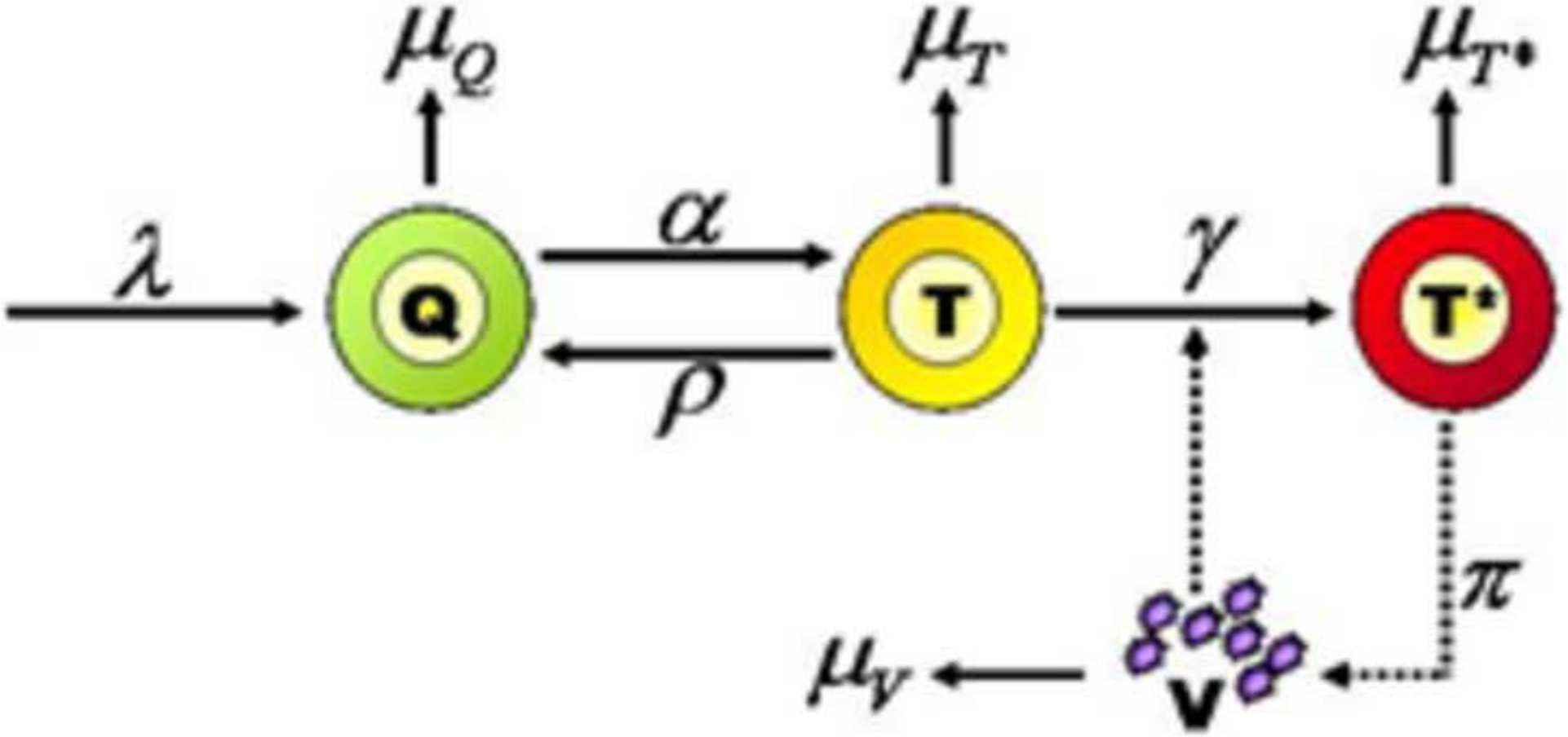

Figure 2

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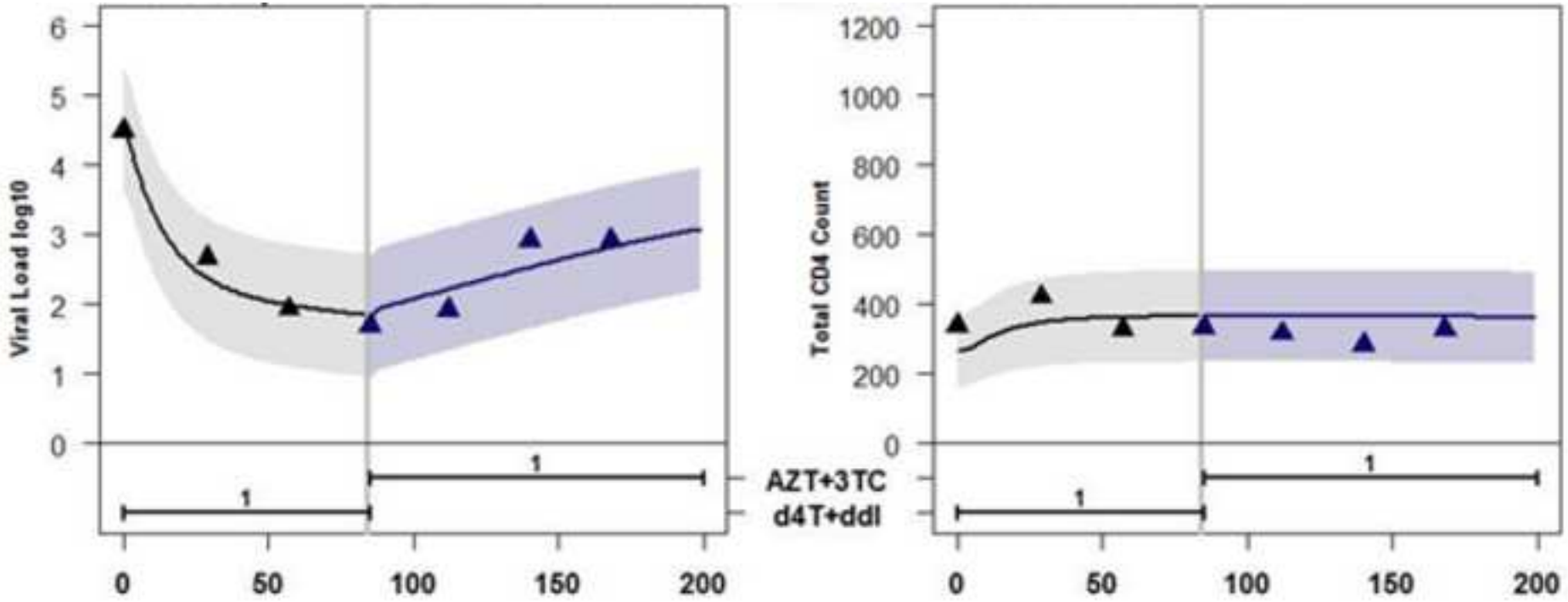

Figure 3

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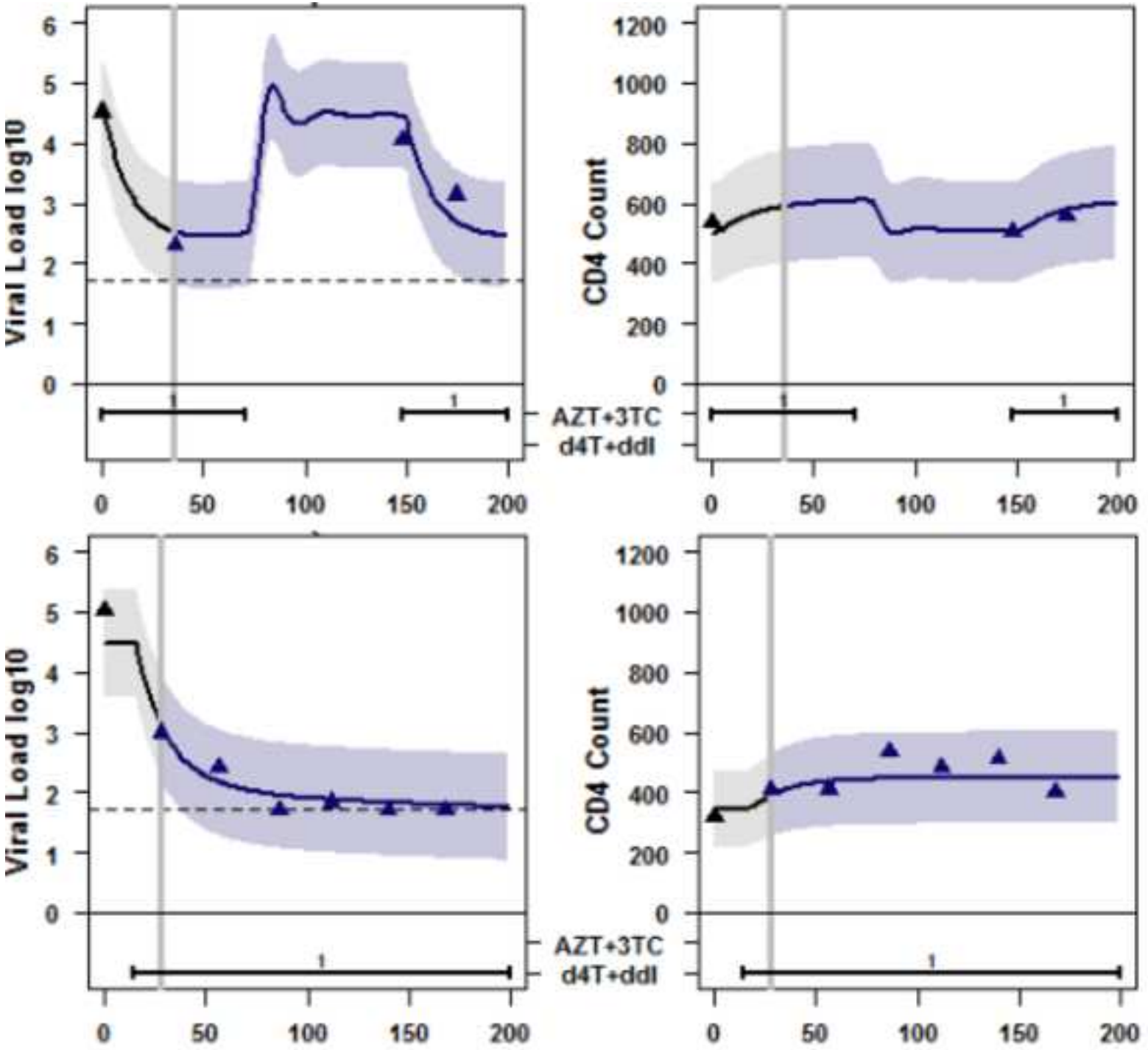

Figure 4a

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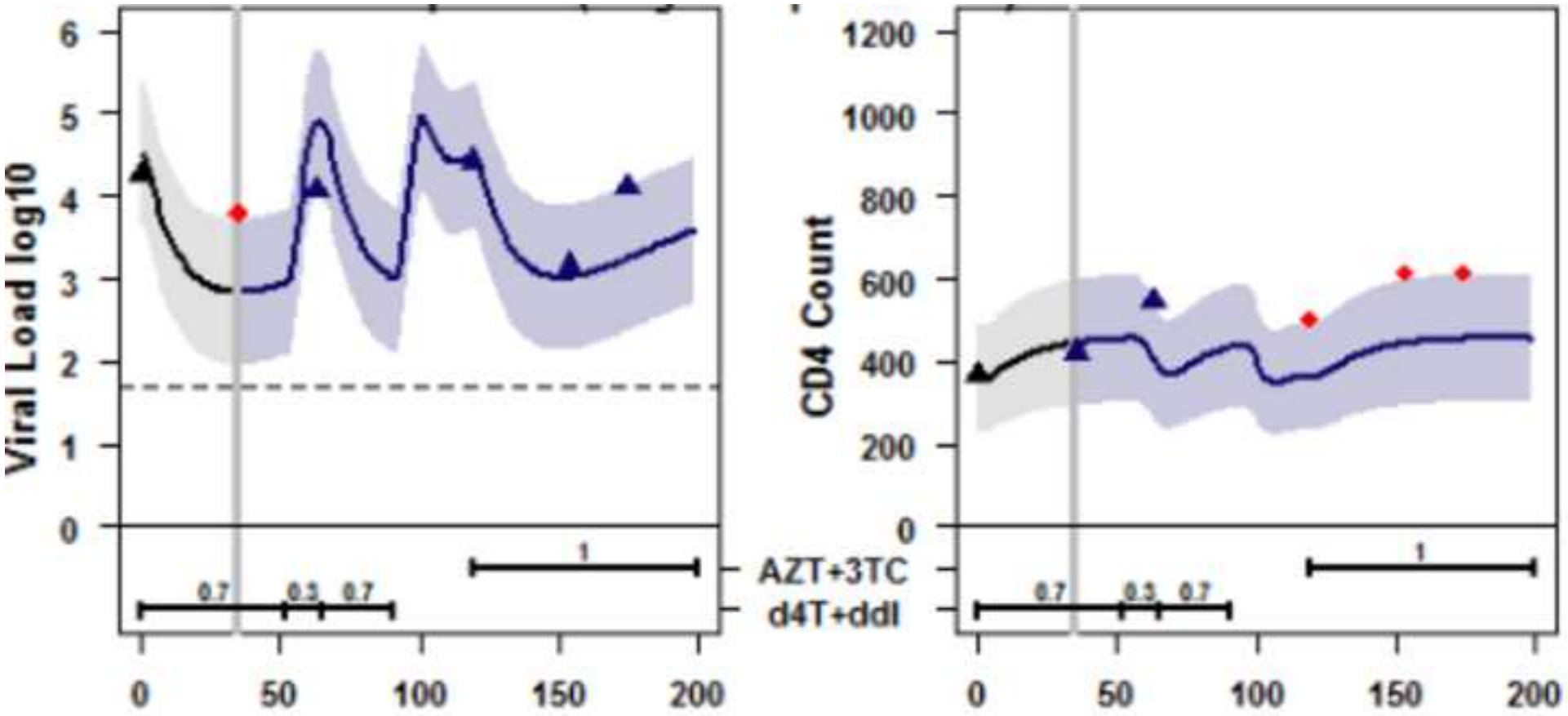

Figure 4b

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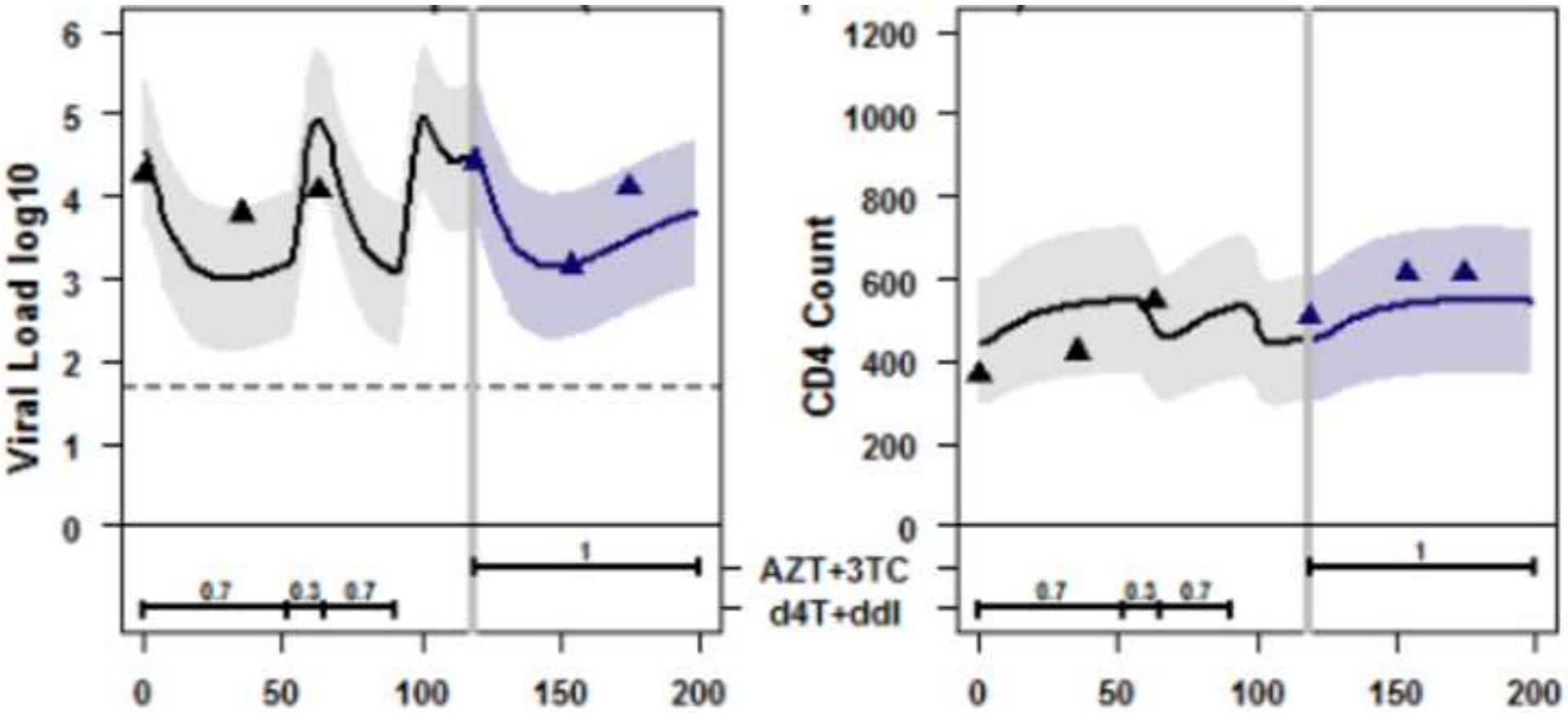

Figure 5

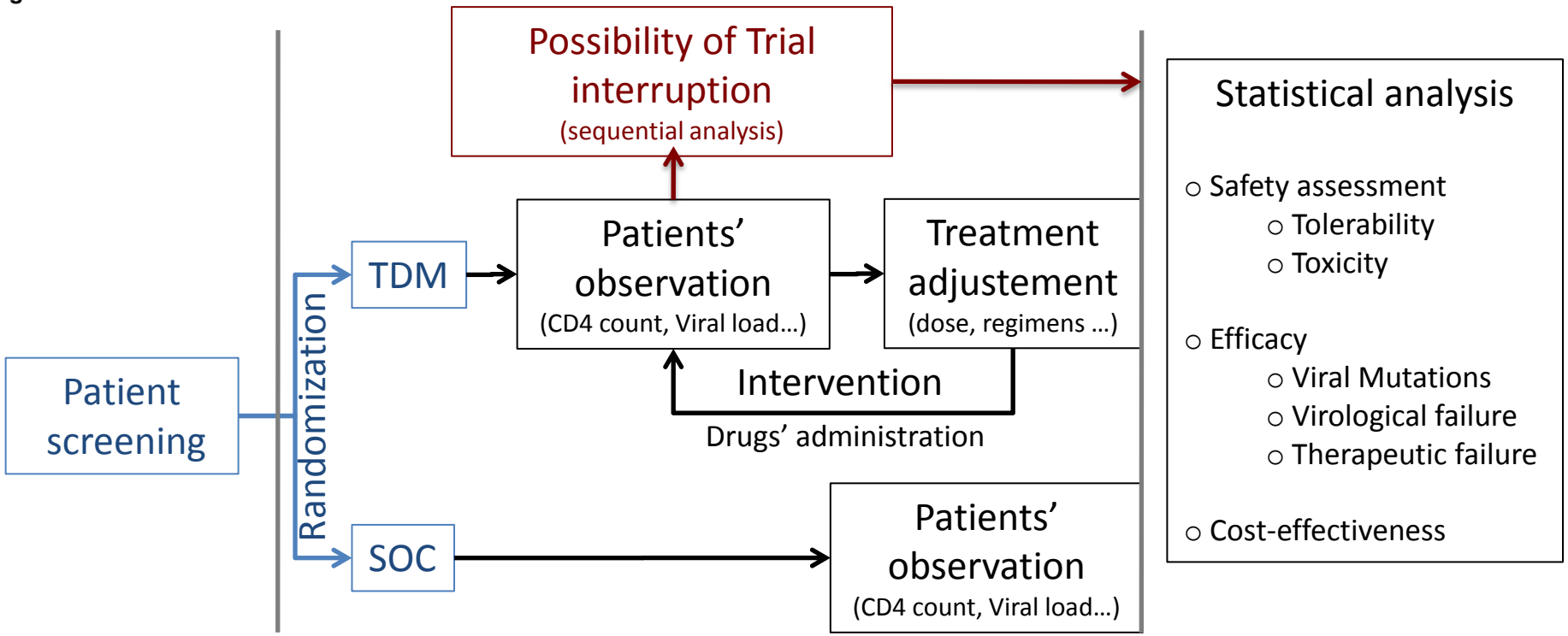
Possibility of Trial interruption
(sequential analysis)
Statistical analysis
○ Safety assessment
○ Tolerability
○ Toxicity
○ Efficacy
○ Viral Mutations
○ Virological failure
○ Therapeutic failure
○ Cost-effectiveness
Patients' observation
(CD4 count, Viral load…)
Treatment adjustement
(dose, regimens …)
TDM
Patient screening
Randomization
Intervention
Drugs' administration
SOC
Patients' observation
(CD4 count, Viral load…)

Table 1 - Biological parameters for the "Activated T-cells model".

Parameter	Meaning
α	Activation rate of Q cells (day^{-1})
μ_{T^*}	Death rate of T^* cells (day^{-1})
λ	Rate of Q cells production ($\mu L^{-1}\ day^{-1}$)
μ_T	Death rate of T cells (day^{-1})
π	Rate of virions per T^* cell (day^{-1})
ρ	Rate of reversion to the Q state (day^{-1})
γ	Infectivity : Infection rate of T cells per virion ($\mu L\ day^{-1}$)
μ_Q	Death rate of Q cells (day^{-1})
μ_V	Death rate of free virions (day^{-1})

Table 2 - PK-PD indicators definition.

PK-PD markers	Meaning	Advantages	Drawbacks
$C_{through}$	Plasma Drug concentration observed after a drug administration and just prior to the administration of a subsequent dose.	* Easy to sample, * Recognized as a standard measure.	* Spatiotemporal, * Few data, * Inter individual variations.
IC_{50}	Drug concentration needed to obtain 50% inhibition of the HIV replication in culture cells.	* Intuitive interpretation - considered as the minimum required level, * Can quantify phenotypic resistances.	* *In vivo* determination is difficult, * Depend on the virus strains.
IQ	$C_{through}/IC_{50}$ The Inhibitory Quotient measures how much the drug exceeds the IC_{50}.	* Include virus susceptibility and individual drug absorption information.	* Based on *in vitro* results, * Not optimal in case of mutations, * Assume linear impact of the dose.
vP	The Virtual Phenotype is the change-fold in IC_{50} for a mutant variant compared to a WT.	* Evaluate individual virus susceptibility, * Account for a mixture of HIV variants.	* Based on *in vitro* results, * High costs and long to run.
vG	The Virtual Genotype is number of expressed listed mutations linked to the considered drug.	* Evaluate individual virus genotype, * Fast to run.	* Need a full understanding and knowledge of virus position of mutations.
vIQ	IQ/vP The Phenotypic Inhibitory Quotient is the IQ for a specific virus strain compared to WT.	* Easy to interpret for a clinician, * No understanding of mutations effects.	* Related with the drugs cut-off, * Low sensitivity to emerging strains.
gIQ	$C_{through}$ / vG The Genotypic Inhibitory Quotient evaluates the effective concentration of the drug.	* Avoid use of IC_{50}, * Sensitive to detect new resistances.	* Values difficult to interpret, * Need to understand gene pathways due to mutations.
D	Drug concentration achieved with a standard dosing.	* Dynamic modeling of drug intake.	* Spatiotemporal Variations, * Difficult to establish which dose is of interest (oral, plasma, intracellular …).
IIP	$log_{10}(1+(D/IC_{50})^m)$ Instantaneous Inhibitory potential measures the antiviral activity accounting for the slope of the inhibition curve (m, the Hill coefficient) depending on the dose.	* Interpretation regarding the replication, * Possible to account for cooperation between drugs, * Differentiate antiretroviral agents classes with m.	* It is unclear whether it is better than IQ *in vivo* to correlate with virologic outcomes ((Henrich et al., 2010; McMahon et al., 2009)).