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Resistance evolution in HIV - modeling when to intervene

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Abstract

The treatment of HIV is complicated by the evolution of antiviral drug resistant virus and the limited availability of antigenically independent antiviral regimens. The consequences to the patient of successive virological failures is such that many strategies to minimize the occurrence of such failures are being investigated. In this paper, a Markov chain-based model of virological failure is introduced. This model considers sequential failure events, and differentiates between several modes of virological failure. This model is then used to evaluate the resistance- targeted interventions by means of testing the impact of a viral load preconditioning strategy on total treatment regimen longevity in HIV patients. It is shown that a proposed intervention targeting pre-existing resistance has the potential to increase the expected time to three sequential virological failures by an average of 3.3 years per patient. When combined with an intervention targeting patient compliance, the total potential increase in the time to three sequential virological failures is as high as 11.2 years. The impact on patient and public health is discussed.

I. INTRODUCTION

Human immunodeficiency virus (HIV) infection is a serious international public health problem that affects over 30 million people worldwide and is associated with high rates of morbidity and mortality [1]. The last 15 years of HIV clinical research have largely focused on development of effective strategies for suppression of HIV replication in a durable and safe manner [2]. HIV infection is now a chronic illness in patients with continued treatment access and excellent long-term adherence [2]. The development of drug-resistant strains of HIV continues to be a primary mode of treatment failure for HIV patients.

Human Immunodeficiency Virus (HIV) is a widespread retrovirus that infects the CD4+ T-Cell, the macrophages and the dendritic cells [3]. The reverse-transcriptase mediated life-cycle of HIV is highly error-prone [4], resulting in a high mutation rate and fast viral evolution [5]. The error rate of HIV-1 reverse transcriptase estimated to be 3.4×10^{-5} substitutions per base pair per replication cycle [6]. Coupled with a high rate of viral turnover (10^{10} virions per day in uncontrolled infection), this results in the rapid evolution of resistant strains. To combat this, HIV is treated with Highly Active Antiretroviral Therapy (HAART), which uses a combination of 3 or more antiretroviral drugs to suppress viral replication while maintaining a high mutational barrier to resistance [1]. HAART

therapy was introduced specifically to prevent the emergence of viral resistance, and studies have found that early treatment with HAART is likely to result in substantially greater benefit [7], [8]. Nevertheless, clinically significant resistance resulting in virologic failure is quite common among patients on HAART [9].

The development of drug resistance remains one of the major barriers to effective long-term treatment of HIV infection [2]. Clinical drug resistance is defined as a non-transient increase in viral load in a treated patient with previously undetectable levels [10]. Patients who continue to receive a failing regimen are likely to accrue multiple antiretroviral drug resistance mutations [11]. The recommended treatment for patients developing drug resistant HIV-1 is a change to a novel regimen with the aim of fully suppressing viral replication, as interruption of antiviral therapy or the continuation of a partially effective regimen significantly compromise long-term prognosis [12], [13]. Genetic testing for antiretroviral drug resistance may be helpful in minimizing the risk of cross-resistance to the new regimen [14]. However, archived drug resistance mutations may not be detected by standard drug resistance tests, which can lead to unanticipated failure even when genetic testing is used.

If resistance develops to every available drug regimen, the patient will be left with few viable treatment options, and may die. Several studies attempting to reduce the risk of resistance emerging during therapy by improving adherence have been undertaken [1], [9], [15], [16]. Failure to adhere to prescribed HIV therapy dramatically increases the risk of developing drug-resistant virus [14], [16]. In previous papers [17]–[21], we have explored the possibility of using failed antiviral regimens to 'precondition' the viral-load, and consequently reduce the incidence of failure due to pre-existing resistant virus.

These various interventions illustrate the fact that viro-logical failure is an event with several known causes [15], [22], each with a probabilistic rate of occurrence. Unanticipated cross-resistance, pre-existing resistant virus, and patient non-compliance are the major reasons for failure of an anti-retroviral regimen [2], [14]. In this paper we develop a Markov chain model describing the sequential events that lead to HIV antiretroviral treatment failure. Transition probabilities and failure times are inferred from data in the available literature. The model is used to evaluate the potential impact of treatment interventions targeting each of the three causes of failure on the average total time until the patient experiences three successive failures. We review similar modeling approaches in Section II. The joint probability of virological failure modeled as a Markov chain of these events is described in Section III. The Markov chain model is used in Section IV to evaluate the overall impact of intervention strategies which target only specific causes of virological failure. Finally, we discuss the implications of these results to patient and public health, and what this implies for future research in Section V.

II. Similar Approaches

Other authors have considered applying Markov modeling to the problem of HIV survival. Deeks et al investigated the time from therapy initiation to first virologic failure (or the duration of success) and the time from first virologic failure to therapy modification. Multivariate Cox regression was used to assess factors associated with time to second

regimen failure and the time to death after the onset of second regimen failure [22]. King et al. [9] constructed a computer simulation model based on observational data to estimate long-term survival in a cohort of HIV/AIDS patients undergoing treatment with HAART. Also, they estimated the treatment failure for each of three rounds of HAART and risk of mortality on-treatment were estimated using parametric survival models with censoring of follow-up fit to the CHORUS trial. Braithwaite et al. used Markov analysis to explain the observed effect of patient adherence on resistance mutation accumulation rate from the HOMER trial [23]. Roberts et al. developed a validated model able to accurately reproduce the time to treatment failure by cycle of therapy and to reproduce the overall survival rate [1].

The four studies listed above show the power of applying Markov analysis to survival data from HIV studies. Our study differs from these previous studies in that it is the first to separately consider the mode of failure due to preexistent resistant virus, and to calculate the potential benefit of treatments affecting this mode.

III. Markov-Chain Model

Anti-retroviral treatment failure in HIV is an adverse event with several known causes [15], [22]. Failure of a regimen is common and can occur for many reasons, including adverse allergic reactions due to altered absorption or metabolism of the drug, cross-resistance, pre-existing resistant virus, and poor patient compliance to the regimen [10].

Some of these causes of virologic failure are determined prior to the introduction of a new regimen, some are dependent on conditions at the time of introduction, and some occur following introduction. Because of their sequential and exclusive nature, these random processes (allergy, cross-resistance, pre-existing resistant and non-compliance-related resistance) may be modeled as a Markov chain. Each cause will be modeled independently in the following sections, and the causes will be combined in a joint model.

The following notation will be used: The virologic failure of a given antiretroviral regimen u_i occurs at a time determined by the random variable T_i after the introduction of u_i . Delays in treatment following failure are clinically dangerous and undesirable [24], [25] and likely of insignificant duration, so they are neglected in this paper. We assume that u_i is introduced at the time when the previous antiretroviral failure occurred T_{i-1} . We also assume that $T_0 = 0$.

There are currently 30 FDA- approved antiviral drugs for use against HIV [25]. Known common cross-resistances between these drugs reduce the number of sequentially usable combinations of these drugs. The index i may be considered to vary between $i = 0$ for a treatment-naïve patient to a maximum value of $i = 7$ for a patient who has exhausted all available antiviral regimens. The maximum index value depends on the particular sequence of regimens chosen, and on average is closer to three than seven [26]. The total time to

failure is $\sum_{i=0}^3 T_i$; it is this quantity which we would like to maximize. The sequential processes and variables in our Markov model of virologic failure are summarized in Figure 1.

A. Allergy

Allergic reactions are random and partially genetically determined [12], [27], and usually occur immediately upon introduction. About 50 % of antiretroviral allergic reactions resolve spontaneously despite continuation of therapy [28]. Therapy should be stopped if symptoms are severe [27], [28]. The allergic reaction usually subsides after discontinuation of the drug [27].

B. Unanticipated Cross-resistance

Cross-resistance is a function of the genetic makeup of the dominant viral strain, and is determined prior to the introduction of the regimen (although appropriate choice of regimen can reduce the incidence of this). The emergence of resistance to one drug often leads to cross-resistance to other drugs of the same family. Cross-resistance is particularly common within the NNRTI class where a single point mutation confers resistance to all NNRTIs [26]. Although the situation is more complicated within the NRTI class, high-level phenotypic resistance to one drug commonly confers partial cross-resistance to most other NRTIs. Low-level NRTI phenotypic resistance is also associated with broad and varying degrees of cross-resistance; however, if regimens are changed before complex mutation patterns emerge, specific sequential regimens within the NRTI class are possible [12]. When drug resistance mutations accumulate, drug susceptibility diminishes and reduces the potency of the components of HAART. The continued replication in the presence of drug will select for even greater levels of resistance and typically leads to cross-resistance to drugs of the same class [29]. Transmission of HIV-1 with reduced susceptibility to antiretroviral drugs may compromise the efficacy of drug therapy [29], making unanticipated cross-resistance possible even in the first regimen.

Adverse allergies and immediate virological failure are often reported together [30]–[34] and both have probability which depend only on prior events. We can therefore model these causes as a single binary random variable C_i . Viro-logical failure occurs immediately if C_i is the cause (and is detected within a month or so), so $T_i|C_i = T_{i-1}$. The overall incidence of C_1 varies in the literature between 0.075 and 0.14 [12], [15], [22], [34]–[36]. In this study, we assume an overall probability of failure by either allergy or cross-resistance of:

$$\begin{aligned} P(C_i) &= 0.1 \\ E(T_i|C_i) &= E(T_{i-1}) \quad (1) \end{aligned}$$

C. Pre-existent Resistant Virus

One of the potential reasons for virologic failure of an antiretroviral regimen is preexisting drug resistance [12]. The high mutation rate of HIV makes it possible that small populations of resistant virus may pre-exist the introduction of therapy, even if they were not selected for by the previous regimen.

The generation of micro-populations of resistant virus is a binomial process. The pre-existing resistant micro-population occurs with a probability proportional to the viral load of the parent strain multiplied by the mutation rate raised to the power of the genetic distance of the parent strain to the resistant strain [37]–[39]. The expected number of resistant virus

present at the introduction of antiretroviral regimen u_i will follow a Poisson distribution, with

$$P\left(r(T_{i-1}) = \frac{n}{VOL} \mid \{v(T_{i-1}), D\}\right) = \frac{\Lambda^n e^{-\Lambda}}{n!}, \Lambda = VOL \times v(T_{i-1}) \mu^D \quad (2)$$

where $\mu = 3 \times 10^{-5} \frac{\text{substitutions}}{\text{replication}}$ is the pointwise mutation rate for HIV, $v(T_{i-1})$ is the viral load of the dominant strain at the introduction of u_i , D is the genetic distance between the dominant strain and the strain resistant to u_i , and $VOL \approx 30$ liters is the effective volume of the human body in ml (converting from viral load measurements, given in units of virus per ml, to total virus in the body). $P(!P_i | C_i)$ is equal to the probability that the number of resistant virus present equal zero, and can be estimated from literature to be between 0.50 to 0.70 [12], [36], [40]–[43] corresponding to a value of $\lambda \approx 0.5$, which corresponds to $D = 2$ and $v(T_{i-1}) = 18,500$ viruses/ml. Therefore,

$$P(P_i) = P(!C_i) \times P((r(T_{i-1}) \neq 0) \mid \{v(T_{i-1}), D\}) \quad (3)$$

If there are a nonzero number of resistant virus present, they will grow in the newly advantageous environment approximately according to Equation 4 as follows:

$$\begin{aligned} \dot{x} &= \lambda - dx - \beta xr \\ \dot{r} &= \beta xr - a_r r \end{aligned} \quad (4)$$

Equation 4 includes the population of CD4+ T cell (x) infected by the population of emerging resistant virus (r) at rate of β . λ representing the regeneration rate of CD4+ T cell and d and a_r are exponential decay rates. The values for these parameters are adapted from [44] Treatment failure occurs at time T_{i-1} when r reaches a certain threshold value R . For small values of r , the solution to these equations is well-approximated by exponential growth at a rate $\frac{\beta\lambda}{d} - a_r$, with initial values taken from the Poisson distribution described above. Based on the values in [44], $\frac{\beta\lambda}{d} - a_r \approx 2.13 \times \text{day}^{-1}$. The approximate failure time associated with an initial population size of resistant mutants $r(T_{i-1})$ is:

$$T_i | P_i = F(r(T_{i-1})) = \frac{\ln(R) - \ln(r(T_{i-1}))}{\frac{\beta\lambda}{d} - a_r} + T_{i-1}. \quad (5)$$

Since $r(T_{i-1})$ is a Poisson random variable that depends on the initial size of the dominant virus population $v(T_{i-1})$ and the genetic distance D , T_i will be a random variable with an expected value

$$E(T_i | \{v(T_{i-1}), D, P_i\}) = \frac{1}{P(!P_i)} \sum_{n=1}^{\infty} F\left(\frac{n}{VOL}\right) \times P\left(r(T_{i-1}) = \frac{n}{VOL} \mid \{v(T_{i-1}), D\}\right) \quad (6)$$

This equation doesn't have a simple closed-form solution, but is easily computed for given values of $v(T_{i-1})$, D . The Poisson parameter λ is dependent on the total number of parent viruses at introduction $v(T_{i-1})$, so both the overall probability $P(P_i)$ and the distribution $T_i | P_i$ may be modulated by strategies which affect the viral load prior to introduction of regimen. Given the above literature approximation $\lambda \approx 0.5$, we will use the values $D = 2$, R

$= v(T_{i-1}) = 18,500$ viruses/ml as our baseline values, and we will assume that interventions exist that can reduce $v(T_{i-1})$ to approximately 50 viruses/ml.

Given these nominal values we have:

$$\begin{aligned} P(P_i | \{V(T_{i-1}) = 18500, D=2\}) &= 0.36, \\ E(T_i | \{v(T_{i-1}) = 18500, D=2, P_i\}) &= T_{i-1} + 9.37 \text{ days} \\ P(P_i | \{V(T_{i-1}) = 50, D=2\}) &= 0.0014 \\ E(T_i | \{v(T_{i-1}) = 50, D=2, P_i\}) &= T_{i-1} + 9.45 \text{ days} \end{aligned} \quad (7)$$

By decreasing the total viral load, the intervention does slightly increase the expected time to failure given the existence of a resistant virus strain, but the overall effect is less than one day. Furthermore, the expected time to failure given pre-existing resistance is much smaller than the expected time to failure due to emerging resistance, so we neglect the impact of this process on T_i and assume $T_i | P_i = T_{i-1}$. If we consider the control input I_1 to represent whether we intervene to reduce the virus load to 50 viruses per mL ($I_1 = 1$), or do not intervene, switching to the new therapy while the virus load is 18500 virus per mL ($I_1 = 0$), then we arrive at a simplified form of the equation for the probability of failure due to pre-existence:

$$\begin{aligned} P(P_i | !C_i) &= \begin{cases} 0.36, & I_1=0 \\ 0.0014, & I_1=1 \end{cases} \\ E(T_i | P_i) &= E(T_{i-1}) \end{aligned} \quad (8)$$

D. Non-Compliance-Related Resistance

Imperfect adherence, or non-compliance, to antiretroviral therapy is the major reason of failure of a durably suppressive antiretroviral regimen [13], [45], [46]. The increased viral replication during missed doses in the presence of residual antivirals results in rapid selection of resistant virus. Risk factors for failure by non-compliance include missed appointments, Complicated drug schedules, younger age, and nonwhite ethnicity [31], [43].

A non-compliance related resistance event is represented as N_i . If a patient has either pre-existent resistant virus or unanticipated cross-resistance, the established strains of the virus would competitively exclude the development of any novel strain due to the non-compliance, so $P(N_i | C_i) = 0$ and $P(N_i | P_i) = 0$, satisfying the Markov Property. By definition:

$$P(N_i) = P(!P_i) + P(!C_i). \quad (9)$$

Modeling the rate of non-compliance is extremely complicated, and data is sparse, so a common simplifying assumption is that non-compliance happens at a relatively constant, population dependent rate [12], [36], [47] following an exponential distribution, with an expected failure time:

$$E(T_i | N_i) = \frac{1}{\lambda_N} \quad (10)$$

In [9], the failure rate λ_N for patients with CD4+ T-Cell counts above 200 cells/mm² was estimated between 0.004 and 0.038 per month. We assume a baseline value of $\lambda_N = 0.0164$ per month for this study, giving us expected time to failure $E(T_i|N_i) = 5$ years. The data from the HOMER trial analyzed in [23] indicates that improved compliance reduces the failure rate, with a relative hazard ratio of 2.73 between poor adherence (65% of doses taken) and optimal adherence (> 95% of doses taken). If we assume that most patients have average adherence, with a hazard ratio of 1.65, then $E(T_i|N_i)$ could be as high as 8.26 years for optimal adherence and as low as 3.03 years for poor adherence. Let I_2 represent the effect of an intervention designed to increase patient compliance, with $I_2 = -1$ representing poor compliance, $I_2 = 0$ representing average compliance and $I_2 = 1$ representing optimal compliance. The equations for the probability of failure by noncompliance-related events can be written as:

$$\begin{aligned} P(N_i) &= 1 - P(C_i) - P(P_i|!C_i)P(!C_i) \\ E(T_i|N_i) &= E(T_{i-1}) + \begin{cases} 3.0 \text{ years, } I_2 = -1 \\ 5.0 \text{ years, } I_2 = 0 \\ 8.3 \text{ years, } I_2 = 1 \end{cases} \quad (11) \end{aligned}$$

E. Combined Markov Chain Model

For each drug regimen u_i , the expected time till failure $E(T_i)$ is, by definition,

$$E(T_i) = P(C_i)E(T_i|C_i) + P(P_i)E(T_i|P_i) + P(N_i)E(T_i|N_i). \quad (12)$$

We neglect the probability of a patient never experiencing virological failure on a given regimen as it is vanishingly small (and, patients dying by unrelated events can be captured in the distribution of N_i). This leads to a Markov Chain event tree with structure shown in Figure 1.

The Markov Chain structure emphasizes the fact that $P(C_i) + P(P_i) + P(N_i) = 1$. An intervention which reduces $P(C_i)$ will proportionally increase $P(P_i)$ and $P(N_i)$. Likewise, an intervention which decreases $P(P_i)$ will proportionally increase $P(N_i)$. It is worth pointing out that interventions affecting compliance do not affect $P(N_i)$ (which is by definition $P(!C_i) + P(!P_i)$). Instead, such interventions affect the expected failure time $E(T_i|N_i)$. By estimating the impact of various intervention strategies on the probabilities and expected failure times.

IV. Strategy Evaluation

We now consider the effects of two possible interventions on the total time before the patient experiences three successive failures. We will not consider interventions that target allergies and unanticipated cross-resistance, so $P(C_i)$ will have a constant value of 0.1. Substituting Equations 1, 8 and 11 into Equation 12 yields a baseline estimate of the expected time to three failures when $I_1 = 0$, $I_2 = 0$ of $E(T_3) = 3 \times (1 - 0.1 - 0.9 \times 0.36) \times 5.0 = 8.6$ years.

We consider interventions of the type described in [18]–[20] to modulate the value of $v(T_{i-1})$, which affects both $P(P_i)$ and $E(T_i|P)$. The methods described in these papers are

theoretically able to consistently reduce $v(T_{i-1})$ from the nominal value of 18,500 virus/ml to less than 50 virus/ml using optimal control-based applications of previously failed antiviral agents. However, as these methods rely on previously failed antivirals, they will only work for the second and third iterations. This yields an estimate to the expected time to three failures when $I_1 = 1$ following the first failure, $I_2 = 0$ of $E(T_3) = (1 - 0.1 - 0.9 \times 0.36) \times 5.0 + 2 \times (1 - 0.1 - 0.9 \times 0.0014) \times 0.5 = 11.9$ years.

As mentioned above, interventions targeting patient compliance could conceivably increase $E(T_i|N_i)$ from 5 years to 8.3 years if they enforced optimal compliance. The expected time to three failures given an intervention that targets only the patient compliance ($I_1 = 0$, $I_2 = 1$) is $E(T_3) = 3 \times (1 - 0.1 - 0.9 \times 0.36) \times 8.3 = 14.3$ years.

Using both interventions together ($I_1 = 1$ after the first failure, $I_2 = 1$) yields an expected time to three failures of $E(T_3) = (1 - 0.1 - 0.9 \times 0.36) \times 8.3 + 2 \times (1 - 0.1 - 0.9 \times 0.0014) \times 8.3 = 19.8$ years.

V. Conclusions

Interventions targeting pre-existent resistance and patient non-compliance can both have significant effects on the length of time to three successive therapy failures for a patient with HIV. In this study, we have used basic principles and nominal values gleaned from the literature to develop a model of sequential virological failures that consider the contribution of unanticipated cross-resistance and allergy, preexisting resistance, and non-compliance associated resistance to virological failure. We used this Markov-chain model in order to evaluate the potential impact of two different types of proposed interventions on the expected time until the patient experiences three sequential virological failures.

The model shows that interventions targeting pre-existing resistance alone can increase the mean time till a patient experiences three consecutive antiviral treatment failures by an average of 3.3 years, from 8.6 years to 11.9 years. This is a significant benefit to the patient in terms of reduced morbidity and mortality associated with multiple treatment failures and rescue therapy.

Treatments that target patient compliance, when used alone, have the potential to increase the expected time to three failures by an average of 5.7 years, assuming they are able to enforce optimal compliance.

The maximum benefits are seen when both interventions are used together. Because the interventions targeting pre-existing resistance work primarily by increasing the likelihood that the patient will experience failure due to a non-compliance related event, these interventions work synergistically with interventions that seek to increase the expected time till a non-compliance related event occurs. Using both interventions together, it is theoretically possible to increase the expected time to three failures by an impressive average of 11.2 years.

VI. Future Work

We have used nominal values for parameters gleaned from the literature. Future work will include further exploration of the published estimates of these parameters, as well as Monte-Carlo analysis of the sensitivity of our results to the various parameters. We also assumed 100% success rates in the interventions targeting pre-existing resistant virus. Future work will explore the sensitivity of our results to a realistic range of estimates for the actual success rates of this intervention. We will also explore the impact of other proposed interventions targeting the development of drug-resistant HIV virus.

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Fig. 1.

Diagram of the Markov model. Antiretroviral treatment (u_i) is introduced at time (T_{i-1}) after the virologic failure of treatment (u_{i-1}). The known causes of virological failure are allergy and cross-resistance (C_i), pre-existing resistant virus (P_i) and non-compliance (N_i) to the regimen.