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Mathematical Modeling of HIV Dynamics After Antiretroviral Therapy Initiation: A Clinical Research Study

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EDITOR: Immunological failure is identified from the estimation of certain parameters of a mathematical model of HIV infection dynamics. This identification is supported by clinical research results from an original clinical trial. Standard clinical data were collected from infected patients starting highly active antiretroviral therapy (HAART) after just 1 month of therapy initiation and were used to carry out the model identification. The early diagnosis is shown to be consistent with patient monitoring after 6 months.

Early Diagnosis of Immunological Failure

Clinical research shows that parameter identification methods constitute an efficient means to characterize critical patients (patients under clinical failure) just 1 month after initiation of a new therapy.[1–3] A clinical trial has been set up for the first time to show that mathematical systems analysis is able to help clinicians in the early diagnosis of immunological failure and in making decisions for treating HIV-infected patients.[3]

The immune potential is given by the maximal level of $CD4^+$ T cells that can be reached if a 100% efficient treatment is administered. This maximal level is obtained by setting the virus load (V) equal to 0 in the first equation of model (2) in reference 4 and computing its equilibrium point (Δ_{max}) as $\Delta_{max} = \frac{s}{\delta}$, where healthy $CD4^+$ cells (T) are produced from the thymus at a constant rate s and die with a half-life equal to $\frac{1}{\delta}$. Patients with a normal thymus function must have a $\Delta_{max} > 200$ CD4/mm^3.[1,4] However, in practice, it is desirable to reach the equilibrium Δ_{max} within a reasonable time (around 6 months in general). Thus, a more restrictive evaluation of the status of the immune system is provided by the time required to reach the critical threshold of 200 CD4/mm^3, denoted as t_{200} (in days). For patients who are not in immunological failure, t_{200} is lower than 6 months. More generally, t_Δ denotes the time required to reach the level Δ of CD4 T cell count in case of 100% efficient therapy. t_Δ is computed as follows (see also reference 3 for more details):

$$t_\Delta = \max\left\{\frac{1}{\delta}\left[-\log_e\left(1-\frac{\delta}{s}\Delta\right)+\log_e\left(1-\frac{\delta}{s}T(0)\right)\right],0\right\}, \quad (1)$$

where $T(0)$ is the initial healthy $CD4^+$ T cell concentration.

Immunological failure is also related to a dysfunctional thymus[3] (characterized by small values of the parameter s), which is unable to produce a sufficient amount of healthy $CD4^+$ T cells. However, it has also been argued that immunological failure is predominantly due to an important activation-induced apoptosis phenomenon (characterized by high values of the activation-induced apoptosis rate A, which appears in the term $-ATT^*$ of the first line of Eq. (2) in reference 4), where T^* is the infected cell concentration and s (CD4 mm^{-3}/day) and A (CD4^{-1} mm^{-6}/day) are parameters of the model.

Summarizing, patients are declared to be *critical* if they belong to one of the following groups:

- A low value of the parameter s ($s \leq 3$) and a high value of the parameter A ($A > 10^{-3}$), or
- $\Delta_{max} < 200$ CD4/mm^3, or
- $\Delta_{max} \geq 200$ CD4/mm^3, but $t_{200} > 6$ months.

Since available measurements typically contain the total (uninfected and infected) $CD4^+$ T cell concentration (T), the concentration of free virions (V), and the concentration of CTL cells (T_{CTL}), the output measurements [for model (2) in reference 4] are $y_1 = T + T^*$, $y_2 = V$, and $y_3 = T_{CTL}$. According

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Table 1. Results of the Estimation of the Values of Parameters s and A

Patient ID	*Initial value of CD4 T cells T (0)*	*Dysfunctional thymus* $s\|_{A=0}$	*Important apoptosis* $A\|_{s=6}$	Δ_{max}	t_{200}
01	376	8.13	1.69E-08	6.25E+02	0
02	230	9.53	1.87E-07	8.533E+02	0
03	**185**	**1.77**	**1.54E-03**	**8.306E+01**	∞
04	205	5.45	4.54E-06	3.761E+02	0
05	383	6.76	6.81E-06	5.551E+02	0
06	405	6.94	1.36E-06	6.644E+02	0
07	*9*	*3.01*	*1.11E-02*	*6.344E+02*	*195.9*
08	122	6.41	9.146E-06	3.727E+02	33.9
09	118	5.36	5.05E-05	3.067E+02	34.4
10	200	4.00	3.36E-04	3.333E+02	3.1
11	**23**	**2.08**	**8.19E-03**	**1.163E+02**	∞
12	310	7.66	7.20E-06	5.610E+02	0
13	**29**	**2.67**	**1.87E-02**	**2.130E+02**	**291.3**
14	140	6.51	1.09E-06	4.049E+02	25.3
15	**63**	**2.29**	**8.43E-03**	**2.767E+02**	**248.7**
16	*3*	*0.61*	*3.51E-01*	*8.654E+02*	*166.5*

The two approaches reveal the same critical patients. Half-life parameters are set to constant values, which are in accordance with typical values published in references 1, 3, and 4. Patients in *bold* are in immunological failure. Patient 16 in *italic* recovered his immunological status due to his young age.

to identifiability theory results presented in reference 5, model (2) in reference 4 is algebraically identifiable from output measurements given by (y_1, y_2, y_3). The computation of the criterion of identifiability[5] shows that at least 15 measurements are needed (5 for y_1, 5 for y_2, and 5 for y_3), *i.e.,* five blood samples are required to compute all parameters of the model. Sensitivity analysis of the parameters against outputs[5] suggests that the first weeks of treatment reveal much more information than other intervals. Therefore, blood measurements were taken during the first 3 weeks after the initiation of treatment. After that, several blood samples were taken to control the prediction of the model and the patient's evolution (see Table 2).

The identification method used in this study was developed and implemented in a software package available online from reference 2. It was based on the Monte Carlo approach, combined with a simplex optimization method. To avoid local optima, random initial conditions were drawn from uniform distributions in the admissible parameter space and corresponding estimates were computed. Using the median and interquartile range of the estimates' distributions, reliable estimations and confidence intervals of the parameters were deduced. For model (2) in reference 4 (with $\eta_1 = 0$), a number of 1,000 randomization was sufficient to obtain stable and robust results.[4] The calibration of the algorithm was as follows:

- Life-time parameters were set to constant values identical to typical values published in reference 4. For instance: $\delta = 0.01\ d^{-1}$.
- Based on the biological characteristics of the infection, the other parameters were constrained to belong to the following intervals: $s \in [1E-5.20]$ and $A \in [1E-20.1]$.
- The uniform distributions U used for the initial conditions were: $U_A \in [1E-10.05]$ and $U_s \in [1E-5.10]$.

Results of the identification of the parameters $s|_{A=0}$, and $A|_{s=6}$[3] are shown in Table 1 for each patient in the EDV05 trial.[2] The primary data collected during the trial are shown in Table 2.

Discussion

The last column in Table 1 displays the theoretical time t_{200} predicted to be necessary to recover a CD4 level above 200 CD4/mm^3. This theoretical time t_{200} was computed from Eq. (1) using parameter identification, based only on the samples from the first 3 weeks after initiation of therapy. According to this theoretical time t_{200}, four patients (in bold in Table 1) are predicted to be in immunological failure since they will not be able to recover the desired CD4 level of 200 CD4/mm^3 within 6 months. The 11 remaining patients are predicted to recover within 6 months, and among those, 10 patients are even predicted to recover the desired CD4 level within 3 months.

Based on the identification of parameters s or A only, six patients are declared to be critical: they are those for whom $t_{200} > 3$ months. Patient 16 (in italic in Table 1) was only 18 years old when he was enrolled in the trial. He had a very low level of 3 CD4/mm^3. This patient was very young and his immunological system demonstrated an ability to recover from its critical status after 6 months as is shown in Table 2. In Table 1, t_{200} was predicted from Eq. (1) to lie within the 3 months range. The last column of Table 2 displays the immunological status of the patients after 6 months. The latter is fully consistent with the above results. The 11 patients reaching the level 200 CD4/mm^3 within 6 months are all correctly identified, which suggests a good sensitivity of the measure based on the identified parameters s and A. The four patients having a level below 200 CD4/mm^3 after 6 months are correctly identified as well, which again suggests a good specificity of the measure. These latter statements deserve an exhaustive statistical study, which is beyond the scope of this trial.

The conclusion from Table 1 is that the identification of the parameters in model (2) in reference 4 as a tool for the early

TABLE 2. CLINICAL DATA COLLECTED IN THE CLINICAL TRIAL DESCRIBED IN REFERENCES 3 AND 4

Patient ID	*Sample 1*	*Sample 2*	*Sample 3*	*Sample 4*	*Sample 5*	*Sample 6*	*Sample 7*	*Sample 8*	*Sample 9*	*Sample 10*	*Sample 11*	*Sample 12*
01 Day CD4	0	1	2	4	11	21	28	45	60	74	91	161
(cells/mm^3) Viral load	376	261	422	524	411	491	398	375	490	582	485	711
[log(copies/ml)]	6.00	6.12	5.65	5.20	3.99	3.47	3.36	2.67	2.59	2.59	2.32	<1.6
02	0	1	2	4	11	18	32	49	60	74	92	183
	230	217	268	208	609	653	547	594	586	565	416	310
	5.40	5.55	5.22	4.59	3.47	3.20	3.19	2.71	2.61	2.55	2.49	<1.6
03	**0**	**1**	**2**	**7**	**13**	**21**	**30**	**45**	**62**	**76**	**91**	**178**
	185	**237**	**305**	**223**	**286**	**181**	**154**	**159**	**60**	**160**	**45**	**179**
	4.54	**4.55**	**4.27**	**3.19**	**2.69**	**2.23**	**1.60**	**1.60**	**1.60**	**1.60**	**1.60**	**<1.6**
04	0	1	2	7	13	20	27	48	62	79	90	167
	205	267	300	355	326	291	270	359	341	320	263	275
	5.30	5.55	5.05	5.28	3.94	3.78	3.70	3.12	2.93	2.95	2.72	1.65
05	0	1	2	4	11	18	32	44	64	74	91	163
	383	413	362	473	427	500	475	376	467	445	467	450
	4.82	4.82	4.50	3.75	3.00	2.83	2.58	2.64	2.21	2.11	1.60	<1.6
06	0	1	2	4	11	21	31	44	59	74	92	199
	405	403	480	522	510	436	479	661	615	445	686	716
	4.97	5.23	5.08	4.35	3.38	3.26	3.08	3.18	2.96	2.46	2.48	<1.6
07	*0*	*4*	*7*	*9*	*11*	*14*	*17*	*29*	*49*	*57*	*92*	*212*
	9	*47*	*68*	*71*	*50*	*42*	*27*	*91*	*9*	*19*	*59*	*116*
	5.07	*4.20*	*3.51*	*3.21*	*2.65*	*2.79*	*2.59*	*2.53*	*5.41*	*4.93*	*2.57*	*2.58*
08	0	4	8	9	11	14	17	30	47	60	91	146
	122	133	177	172	208	174	231	201	251	262	276	207
	5.38	4.57	3.93	3.76	3.64	3.31	3.12	2.78	2.74	2.42	1.60	<1.6
09	0	4	7	11	15	17	29	45	59	X	94	185
	118	233	248	252	212	184	228	207	235	X	356	407
	5.21	4.43	3.87	3.50	3.41	3.20	3.08	2.76	2.52	X	1.91	<1.6
10	0	4	7	9	11	14	18	32	46	60	91	X
	196	2.91	251	238	231	360	247	163	256	262	221	X
	5.3	4.36	4.12	4.00	3.50	3.47	3.52	2.80	3.44	2.68	4.80	X
11	**0**	**4**	**7**	**8**	**11**	**14**	**18**	**31**	**45**	**60**	**88**	**171**
	2.3	**40**	**38**	**57**	**30**	**52**	**55**	**63**	**85**	**78**	**72**	**103**
	6.20	**5.18**	**4.20**	**4.07**	**3.61**	**3.23**	**3.17**	**2.81**	**2.60**	**2.42**	**2.10**	**2.02**
12	0	4	7	9	11	14	17	29	45	57	85	176
	305	408	337	383	415	430	411	418	463	458	426	603
	5.7	4.23	3.58	3.32	3.18	3.16	3.00	2.60	2.50	2.17	1.82	<1.7
13	**0**	**4**	**7**	**9**	**11**	**15**	**18**	**29**	**46**	**63**	**91**	**179**
	29	**39**	**46**	**47**	**32**	**24**	**59**	**85**	**95**	**90**	**130**	**172**
	5.22	**3.89**	**3.23**	**3.20**	**3.08**	**3.12**	**3.27**	**3.05**	**2.40**	**2.24**	**2.03**	**1.92**
14	0	4	7	9	11	14	17	29	45	57	84	175
	139	143	145	145	182	211	201	224	197	264	262	326
	5.66	4.79	4.48	4.29	4.27	4.05	4.07	3.13	2.41	2.19	2.17	1.72
15	**0**	**4**	**7**	**9**	**11**	**14**	**17**	**30**	**45**	**63**	**91**	**135**
	63	**40**	**25**	**34**	**52**	**84**	**75**	**63**	**58**	**55**	**108**	**42**
	5.22	**4.37**	**4.01**	**3.59**	**4.02**	**3.58**	**3.21**	**3.00**	**2.38**	**2.38**	**2.07**	**6.58**
16	*0*	*4*	*7*	*9*	*11*	*14*	*16*	*29*	*45*	*60*	*88*	*186*
	3	*3*	*4*	*5*	*3*	*10*	*20*	*16*	*28*	*67*	*157*	*227*
	5.12	*5.05*	*5.04*	*4.63*	*4.71*	*5.05*	*4.82*	*4.39*	*4.38*	*3.77*	*3.17*	*3*

Eleven samples were used for the estimation of parameters and the prediction of the immunological status. One more sample was taken, 6 months after the beginning of the trial, to verify the predicted immunological status. Patients in *bold* are in immunological failure. Patient 16 in *italic* recovered his immunological status due to his young age.

diagnosis of immunological failure immediately after the first month following the initiation of a new therapy is useful and very effective. However, the peculiarities of each patient must be taken into account by the physician to make a final clinical decision. For future work, different avenues of research could be explored using methods relying on mathematical analysis and systems and control theory, e.g., the diagnosis of irreversible treatment failure, confirmation of resistance, and identification of patients who are likely to be more vulnerable to the level of adherence.

Author Disclosure Statement

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