A computational lymph tissue model for long term HIV infection progression and immune fitness

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Abstract. Given the complexity of biological systems, modelling the immune response to the spread of infectious disease is non-trivial and has been the subject of considerable computational efforts. HIV infection, if untreated, leads to a slow depletion of the immune system over many years, resulting in terminal AIDS disease and death. Despite decades of research, the biological mechanisms underpinning the immune system response and implicit in its impairment remain a subject of discussion. Recent biological findings indicate the importance of functional lymphatic tissue in maintaining homoeostasis of the immune system, which is vital for stability. HIV infection-related immune activation leads to chronic inflammation of this tissue and formation of non-functional scar tissue with detrimental effects on homeostasis. We propose a computational model based on the Cellular Automata formalism to quantify these effects in a simulated fraction of a lymphatic tissue. We also include effects of antiretroviral treatment and highlight implications for system representation through larger-scale simulations, as well as optimizations of treatment schedules.

Keywords: HIV, computational model, Cellular Automata, antiretroviral treatment

1 Introduction

1.1 HIV infection

Acquired Human Immunodeficiency Syndrome (AIDS) remains a global health concern even three decades or more after the discovery of the Human Immunodeficiency Virus as its root cause, [1]. The virus preferentially infects white blood cells of a certain type (CD4+), which are a crucial part of the immune response, leading to failure of the immune system approximately 10 years after initial infection. Potent drugs, termed Antiretroviral Therapy (ART), have been developed, which aim at the suppression of viral activities. However, these medications do not provide a cure for the disease, due to the persistence of impermeable viral reservoirs in the body; instead they have to be administered life-long to maintain sufficient viral suppression, [2]. Daily administration of

multiple drugs can become a problem and interruptions are common, especially in resource-limited settings, where drug availability is not guaranteed or social factors interfere with adherence, [3].

Moreover, Structured Treatment Interruptions (STIs) have been suggested to enable recovery from drug toxicities, to promote resilience of the immune system and to reduce drug costs, [4]. Though initial clinical studies on STIs provided encouraging evidence regarding safety of interrupted treatment, [5, 6], a subsequent large-scale study (SMART) indicated potential harmful effects, [7]. Despite these effects have not been characterized in detail and may have been related to study design, [8], the results led to a general loss of interest in assessing treatment interruptions in a clinical setting. Questions regarding safe margins of interruption regimen and the nature of detrimental effects thus remain open.

1.2 Lymphatic tissue involvement

It is well-known that viral replication occurs predominantly in lymphatic tissue, where most of the susceptible cells are located, [9]. The lymphatic system is a widespread network of nodes and ducts which is crucial for immune response but also for the spread of infected cells throughout the body.

Recent advances in *in-vivo* microscopy have enabled determination of the detailed structure of a certain kind of lymphatic tissue, the Fibroblastic Reticular Cell Network (FRCn). Its mesh-like structure has been reported to mimic a small world topology with lattice-like properties, [10]. This view is complemented by histological imaging showing that the Fibroblastic Reticular Cells (FRCs) are fixed to a scaffolding of collagen fibers. During inflammation, this formation of collagen fibers is greatly increased, [11], leading to collagen deposits (see Fig. 1) which block off FRCs from the chemical signals (cytokines) which maintain their viability, leading to depletion of these cells and formation of non-functional collagen tissue. Antiretroviral treatment has been shown to stop the formation of the scar tissue but not to enable its reversal, [12]. The formation of FRCn has not yet been observed *in vivo* due to the long timescales involved (weeks to years), however.

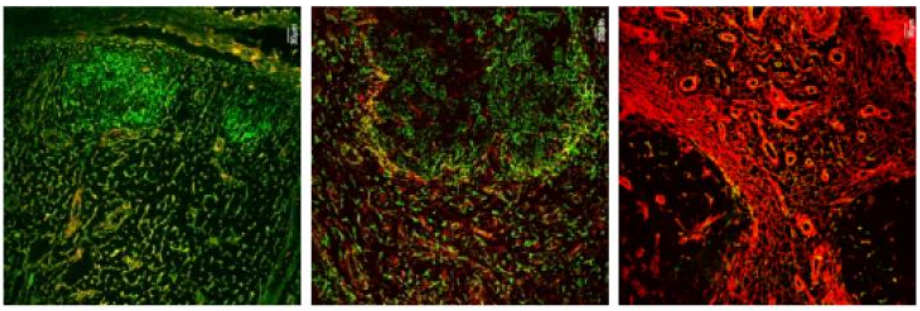

Fig. 1. Distinct stages of collagenation of lymphatic tissue for uninfected, early, and late stage HIV infection (from left). Green staining denotes functional tissue, red non-functional collagen. Image source: [12].

1.3 Modelling approaches

Various models have been proposed in the HIV context to help understanding the spread of the virus between, [13], and within hosts, [14]. The majority of these models have found to be based on systems of Ordinary Differential Equations (ODEs), [15], representing a variant of the SIR model originally used to model spread of communicable diseases throughout populations. In context of within-host models, each DE denotes the change of a quantitative property related to HIV like viral load, healthy and infected cell concentrations over time. Starting from basic forms with two or three equations, models have been extended to cover additional features, like effects of antiretroviral treatment or immune response (resulting in systems of 20 or more equations). Simpler forms allow further mathematical analysis, [16], whereas more complex forms may be used for numerical simulation studies, [17]. For a more detailed review on ODE based HIV-modelling see [14] and references therein.

In general, ODE-based approaches assume virus und susceptible cells being in an environment satisfying the conditions of *well-mixed*. That assumption fits loosely best to the bloodstream, which initially has been considered a main source of viral replication, [14]. However, following the increasing availability of data on tissue involvement, the suitability of the well-mixed assumption has been questioned recently, [18].

Treatment interruptions and optimizations have also been subject to modelling studies using ODEs, [15]. A popular approach, besides pure simulation studies, [19], considers an optimal control problem, [20–22], to obtain treatment regimen which keep biological properties, like viral load or healthy cell count within predefined bounds which are considered to be non-critical. This view of the biological system as a kind of thermostat was especially useful with only limited data on anatomical compartments other than the bloodstream available. However, as clinical studies have indicated the complexity of HIV infection progression, consideration of alternative modelling approaches might be worthwhile.

We therefore propose a computational model, which considers both spatial structure of lymphatic tissue and the effects of inflammation, to examine long-term development and to allow predictions to be made on effects of treatment interruptions, where clinical data is not available for reasons mentioned in section 1. Our model presents an extension of the approach reported in [15] with improved biological realism obtained from drawing upon recent studies.

2 Methods - Numerical simulations

2.1 Surrounding conditions

For our model we assume two effects to be responsible for the depletion of CD4+ cells, as reported by clinical studies, [11].

- HIV-induced direct killing of susceptible CD4+ cells
- Impairment of survival through depletion of FRCs

Both factors influence the concentration of CD4+ cells in the body, with the time-scale of the former relatively short (days to weeks) while the latter is effective at longer time-scales (months to years). However due to regenerative capabilities of CD4+ cells, the first effect is reversible under antiretroviral treatment, while only minimal regeneration has been observed, [12], for the second.

We apply a bottom-up modelling approach, by using the Stochastic Cellular Automata (SCA) formalism, i.e. a stochastic extension of Cellular Automata (CA), [23]. The CA formalism has successfully been applied for modelling environments involving fixed matrices, including HIV, [24]. It utilizes a regular grid or lattice structure, where each site represents a single cell and its neighborhood the cell-to-cell contacts. We further assume that each cell has a connection to its 4 immediate neighbors as suggested from analysis of *in-vivo* imaging data, [10]. In terms of Cellular Automata computation, this corresponds to a *von Neumann* neighborhood.

An average lymph node measures about 1 cm in diameter and is of approximately spherical shape. From murine experiments, it is known that in FRCn, mean separation of the centers of mass of single cells is ~ 23 μm, [10]. A human lymph node, would therefore consist of around 40 Million FRCs. For our simulations, however, we consider a smaller fraction, namely a 2-dimensional slice through a lymph node, consisting approximately of 250,000 single cells. This slice represents less than 1% of the total volume, however this simplified view is acceptable in this case since we do not aim at reproducing an anatomically correct representation of the organ (see e.g. [25]).

From clinical data, we know that collagenation mainly starts from connections in the blood circulation (High Endothelial Venules). These connections appear to be scattered randomly throughout the tissue, [12]. We assume that collagenation increase occurs predominantly through elongation of existing collagen fibers as suggested by those data available to date on this aspect.

2.2 Model rules

Before simulated infection occurs, the lattice is populated with both healthy FRCs and co-located CD4+ cells. The CD4+ cells are assumed to maintain equilibrium (homeostasis) and their concentrations in lymphatic tissue to be stable, [26]. However, HIV infection has a two-fold effect in our model: destroying CD4+ cells through viral infection and mechanisms of cellular apoptosis and pyroptosis, and through upregulation of the immune system, [26]. The upregulated immune response in turn causes increased collagenation of lymphatic tissue.

The fraction of CD4+ cells which is co-located with collagenated tissue, tends to exhibit poorer survival than usual (in healthy tissue), in addition to the depletion due to HIV infection. Treatment, however reduces the latter, as well as inflammation stimulation, since viral load is reduced. CD4+ cells are therefore regenerated and the collagenation processes in lymphatic tissue are slowed down. Upon reinstatement of upregulation of the immune system due to a treatment interruption, however, homeostasis disruption occurs again.

In terms of model rules, no direct death and/or inflammation takes place other than by viral infection. This context gives rise to the state transition model shown in Fig. 1,

which contains the four possible combinations of CD4+ cells and collagen status as well as permitted changes.

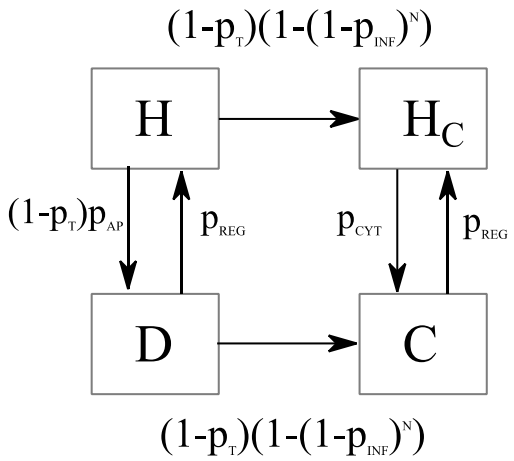

Fig. 2. Block diagram of state changes of the SCA with probabilities of transitions, where applicable (for details see Table 1.). H: healthy CD4+ cell; H_C: healthy CD4+ cell co-located with collagen; D: dead CD4+ cell (empty); C: empty site co-located with collagen.

As mentioned in the previous section, collagenation originates from the High Endothelial Venules, where CD4+ cells enter the lymph nodes from the blood circulatory system. The assumption, that the blood circulation acts as a means to spread infection throughout the body, allows us to calibrate the model using available clinical data on CD4+ cell long-term degradation under HIV infection, obtained from blood samples, [27]. Table 1 lists the model parameters together with values obtained by calibration.

Table 1. Model parameter value selection

Parameter	Description	Default value
P_T	Treatment effectiveness	0.9
P_{INF}	Infection induced inflammation, drives collagenation	0.1
P_{REG}	CD4+ cell regeneration	0.3
P_{CYT}	CD4+ cell death due to signaling (cytokines)	0.9
P_{AP}	CD4+ cell death through infection (apoptosis)	0.1
N	Collagenated neighbors	1 - 4

2.3 Simulation setup

Using the model parametrization in this table, we aim to test the effect of different patterns of *unstructured* interrupted treatment in the long term on collagenation (and

thus immune system degradation). To simulate interrupted treatment, we assume 'average' adherence (the probability that the simulated patient takes the medication each week). As the treatment initiation timing has also been deemed to be important in clinical studies, [28], we allow for this in the simulations as well. Table 2. summarizes the parameter values chosen for the simulation runs. After the treatment period (corresponding to ~ 5 years), the increase in collagenation compared to that evident at the start of treatment is determined.

Table 2. Simulation parameters

Description	Value range
Time step	1 week
Treatment initiation	0, 50, 100, 150, 200 time steps
Treatment adherence	0%, 20%, 40%, 60%, 80% 100%
Treatment period duration	250 time steps
Total simulation length	500 time steps (~ 10 years)

In a second experiment, we aim to investigate the effects of *structured* treatment interruptions. Thus, we adopt the approach of *CD4+ guidance*, which has been pursued in recent clinical trials, [4].This approach uses a threshold value of CD4+ cell count in a patient as a *surrogate marker* to decide on interruption or (re-)initiation of antiretroviral treatment. For our simulations, we apply the limits used in two major clinical trials, [7, 29] and again observe the outcomes after 500 time steps.

3 Results and Discussion

3.1 Unstructured interruptions

An example model run is depicted in Fig. 3, exhibiting *unstructured* treatment interruptions due to incomplete adherence. In general, the model runs demonstrate good correspondence to clinical results, [6]. For an infection simulated to occur at time step 0, the count of CD4+ cells drops rapidly, (characteristic of the acute phase). The cell count continues to drop at a slower rate until initiation of simulated treatment, which leads to a significant recovery in number of CD4+ cells. Incomplete adherence to the treatment regime causes temporary drops in cell numbers (signified by the irregular saw tooth pattern), as well as an overall decline in the long term. This decline accelerates once the treatment period concludes. Collagenation, however, exhibits a constant increase, albeit with less-pronounced slope during treatment.

In Fig. 4 we show the loss of CD4+ cells and the increase in collagenation during treatment periods. The results illustrate the influence of treatment initiation timing and of adherence to the regimen. We observe that the latter has a fundamental impact on long-term progression of collagenation and, consequently, on immune system fitness.

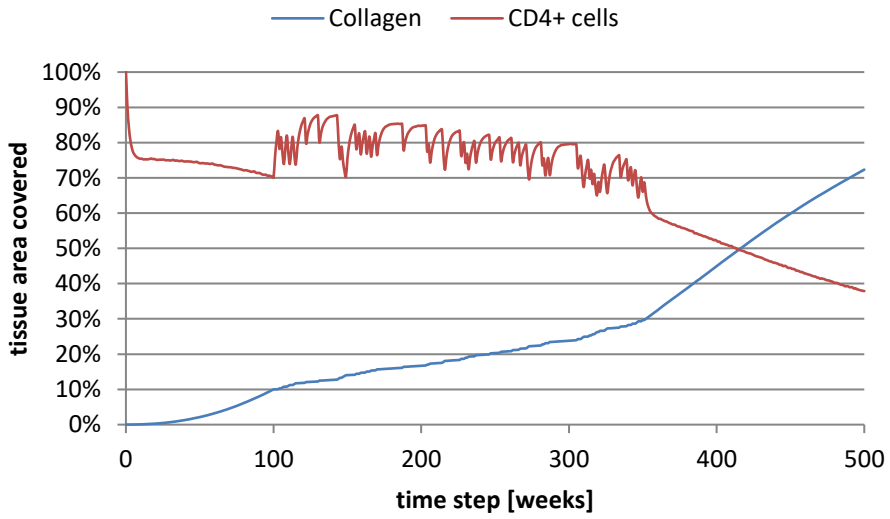

Fig. 3. Time course of collagenation (blue line) and population of CD4+ cells (red line) during a period of interrupted treatment (100 to 350 time steps; 0.8 adherence)

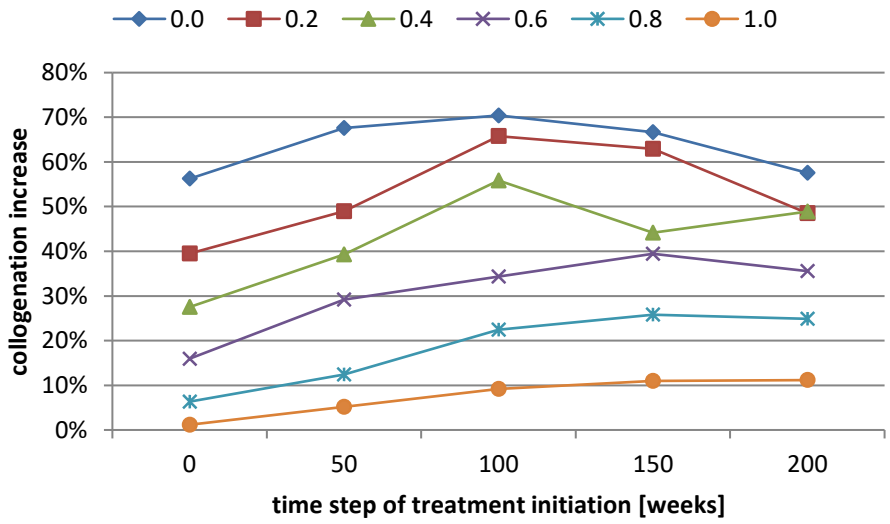

Fig. 4. Effect of different adherence levels (lines) and treatment initiation on collagenation increase at end of treatment period.

Treatment initiation timing has a less-pronounced effect. Results show that, if treatment is introduced during the early phases of infection (within the first 2 years), initiation time has greater impact than for later stages. However, with high adherence (80% and

above), collagenation can be kept within acceptable bounds even for late treatment initiation. As an acceptable outcome, we take a total collagenated area of less than 75% at the end of the simulated 10 years. This level has been determined as a threshold from clinical data, [12], above which AIDS disease is imminent.

3.2 Structured interruptions

Example results of our second experiment concerning *structured* treatment interruptions are shown in Fig. 5. Using the same thresholds for CD4+ guidance as two large-scale clinical studies (SMART, LOTTI, see Table 3.), simulated data is in good correspondence with clinical data. The two sets of clinical data indicate that counts of CD4+ cells are constantly decreasing during the course of these studies, reflected by the simulation data. Since the duration of the clinical trials was limited due to practical reasons, we extended simulation times to allow for an estimation of long-term effects of the interruption thresholds used in the studies.

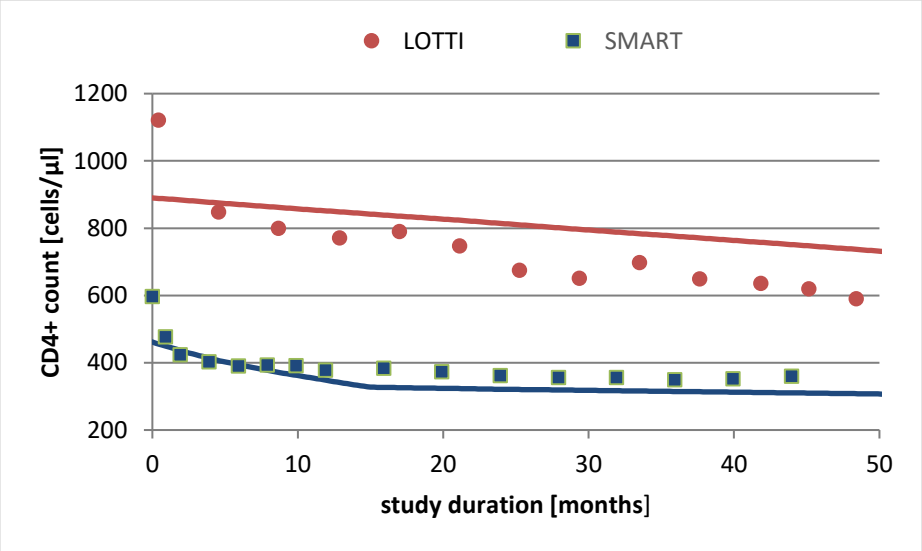

Fig. 5. Comparison of clinical data from two CD4+ guided STI studies (LOTTI, SMART; dots) with model output (lines) from corresponding simulation experiments.

On this behalf, absolute values of CD4+ count limits from clinical literature were normalized for use with the model by assuming an initial cell count of 1000 cells/µl.and results were again obtained after 500 time steps (~ 10 years). The results (see Table 3.) show a relatively small difference both in terms of collagenation and CD4+ counts. These results are remarkable in a way since the SMART study strongly indicated adverse effects of interrupted treatment, whereas the LOTTI study did not find significant differences in this regard compared to continuous treatment. The different outcomes of

our simulations in terms of collagenation and CD4+ count may therefore account for some threshold between non-critical progression and adverse effects.

Table 3. Experimental results for CD4+ guided structured treatment interruptions

	CD4+ count limits [cells/µl]		Simulation results (~ 10 years)	
Clinical study	Interruption	Resumption	Collagenation	CD4+ count
SMART [7]	350	250	97%	260
LOTTI [29]	700	350	81%	380

4 Conclusion

We have proposed a simple Stochastic Cellular Automata model, which describes the effects of HIV infection and antiretroviral therapy on both CD4+ cell counts and collagen deposition in lymphatic tissue. Additionally, the model can predict possible outcomes of incomplete antiretroviral treatment, both unstructured and structured (difficult to obtain from controlled clinical studies). Simulated *adherence patterns* indicated the importance for long-term immunological fitness, of overall adherence to medication, and of treatment initiation timing during the early phases of infection, with regard to improved management. These experiments on antiretroviral treatment timing and adherence explore the implications for outcomes of *Structured Treatment Interruptions*, formerly discounted due to lack of long term predictions, despite some evident patient benefits.

Further steps might include an extension of our approach to evaluate strategies for an improved monitoring of antiretroviral therapy by helping to identify patterns, like certain concentration thresholds, which may indicate a future loss of viral control given poor adherence by employing AI techniques. Applicability in real-life settings may furtherly be improved by incorporation of realistic sampling intervals to obtain biological properties from blood or tissue with least patient stress.

Regarding structured interruptions, numerical simulation in conjunction with appropriate optimization techniques could be utilized for identifying optimal treatment regimen with improved biological realism compared to ODE-based approaches. A conceivable way would be the use of evolutionary algorithms to optimize treatment on/off patterns.

In addition, the proposed model offers further development potential, not least as it represents to date only a small part of human lymphatic tissue. A realistic simulation size even for one lymph node requires around 100 times more lattice sites than the current model. This problem can be alleviated using state-of-the-art parallelization approaches, [30], to simulate different regions and this forms part of ongoing investigation.

Unfortunately, clinical data for validation of model performance are sparse at present due to ethical considerations as well as measurement limitations, but recent advances in biological imaging and *in-vivo* microscopy may well provide additional insights and enable refinement of key parameters.

In summary, computational modelling of lymphatic tissue features involving cell-to-cell connections offers considerable potential for further investigation and optimization of long-term HIV treatment. Promising foundations using bottom-up modelling have already been laid for investigating infectious diseases. We think it worthwhile to pursue further, given growing availability of appropriate experimental and clinical data.

References

1. Barré-Sinoussi, F., Chermann, J.C., Rey, F., Nugeyre, M.T., Chamaret, S., Gruest, J., Dauguet, C., Axler-Blin, C., Vézinet-Brun, F., Rouzioux, C., Rozenbaum, W., Montagnier, L.: Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science. 220, 868–871 (1983).
2. WHO: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, http://www.who.int/hiv/pub/guidelines/arv2013/download/en/.
3. Mann, M., Lurie, M.N., Kimaiyo, S., Kantor, R.: Effects of political conflict-induced treatment interruptions on HIV drug resistance. AIDS Rev. 15, 15–24 (2013).
4. Benson, C.A.: Structured treatment interruptions--new findings. Top. HIV Med. 14, 107–11 (2006).
5. Rosenberg, E.S., Altfeld, M., Poon, S.H., Phillips, M.N., Wilkes, B.M., Eldridge, R.L., Robbins, G.K., D'Aquila, R.T., Goulder, P.J., Walker, B.D.: Immune control of HIV-1 after early treatment of acute infection. Nature. 407, 523–526 (2000).
6. Dybul, M., Chun, T.W., Yoder, C., Hidalgo, B., Belson, M., Hertogs, K., Larder, B., Dewar, R.L., Fox, C.H., Hallahan, C.W., Justement, J.S., Migueles, S.A., Metcalf, J.A., Davey, R.T., Daucher, M., Pandya, P., Baseler, M., Ward, D.J., Fauci, A.S.: Short-cycle structured intermittent treatment of chronic HIV infection with highly active antiretroviral therapy: effects on virologic, immunologic, and toxicity parameters. Proc. Natl. Acad. Sci. U. S. A. 98, 15161–6 (2001).
7. Siegel, L., El-Sadr, W.: New perspectives in HIV treatment interruption: The SMART study. PRN Noteb. 11, 8–9 (2006).
8. Hirschel, B., Flanigan, T.: Is it smart to continue to study treatment interruptions? AIDS. 23, 757–759 (2009).
9. Pantaleo, G., Graziosi, C., Demarest, J.F., Butini, L., Montroni, M., Fox, C.H., Orenstein, J.M., Kotler, D.P., Fauci, A.S.: HIV infection is active and progressive in lymphoid tissue during the clinically latent stage of disease. Nature. 362, 355–358 (1993).
10. Novkovic, M., Onder, L., Cupovic, J., Abe, J., Bomze, D., Cremasco, V., Scandella, E., Stein, J. V., Bocharov, G., Turley, S.J., Ludewig, B.: Topological Small-World Organization of the Fibroblastic Reticular Cell Network Determines Lymph Node Functionality. PLOS Biol. 14, e1002515 (2016).
11. Schacker, T.W., Reilly, C., Beilman, G.J., Taylor, J., Skarda, D., Krason, D., Larson, M., Haase, A.T.: Amount of lymphatic tissue fibrosis in HIV infection predicts magnitude of HAART-associated change in peripheral CD4 cell count. AIDS. 19, 2169–2171 (2005).

12. Zeng, M., Southern, P.J., Reilly, C.S., Beilman, G.J., Chipman, J.G., Schacker, T.W., Haase, A.T.: Lymphoid Tissue Damage in HIV-1 Infection Depletes Naïve T Cells and Limits T Cell Reconstitution after Antiretroviral Therapy. PLoS Pathog. 8, e1002437 (2012).
13. May, R.M., Anderson, R.M.: Transmission dynamics of HIV infection. Nature. 326, 137–142 (1987).
14. Perelson, A.S., Nelson, P.W.: Mathematical Analysis of HIV-1 Dynamics in Vivo. SIAM Rev. 41, 3–44 (1999).
15. Hillmann, A., Crane, M., Ruskin, H.J.: HIV models for treatment interruption: Adaptation and comparison. Phys. A Stat. Mech. its Appl. 483, 44–56 (2017).
16. Pawelek, K. a., Liu, S., Pahlevani, F., Rong, L.: A model of HIV-1 infection with two time delays: Mathematical analysis and comparison with patient data. Math. Biosci. 235, 98–109 (2012).
17. Sun, Q., Min, L.: Dynamics Analysis and Simulation of a Modified HIV Infection Model with a Saturated Infection Rate. Comput. Math. Methods Med. 2014, 1–14 (2014).
18. Cohen, J.: Tissue Says Blood Is Misleading, Confusing HIV Cure Efforts. Science (80-.). 334, 1614–1614 (2011).
19. Ferreira, J., Hernandez-Vargas, E. a., Middleton, R.H.: Computer simulation of structured treatment interruption for HIV infection. Comput. Methods Programs Biomed. 104, 50–61 (2011).
20. Adams, B.M., Banks, H.T., Kwon, H.-D., Tran, H.T.: Dynamic multidrug therapies for hiv: optimal and sti control approaches. Math. Biosci. Eng. 1, 223–241 (2004).
21. Krakovska, O., Wahl, L.M.: Optimal drug treatment regimens for HIV depend on adherence. J. Theor. Biol. 246, 499–509 (2007).
22. Rivadeneira, P.S., Moog, C.H., Stan, G.-B., Brunet, C., Raffi, F., Ferré, V., Costanza, V., Mhawej, M.J., Biafore, F., Ouattara, D. a., Ernst, D., Fonteneau, R., Xia, X.: Mathematical Modeling of HIV Dynamics After Antiretroviral Therapy Initiation: A Review. Biores. Open Access. 3, 233–241 (2014).
23. von Neumann, J.: Theory of self-reproducing automata. Inf. Storage Retr. 5, 151 (1969).
24. Wodarz, D., Levy, D.N.: Effect of different modes of viral spread on the dynamics of multiply infected cells in human immunodeficiency virus infection. J. R. Soc. Interface. 8, 289–300 (2011).
25. Kislitsyn, A., Savinkov, R., Novkovic, M., Onder, L., Bocharov, G.: Computational Approach to 3D Modeling of the Lymph Node Geometry. Computation. 3, 222–234 (2015).
26. Fletcher, A.L., Acton, S.E., Knoblich, K.: Lymph node fibroblastic reticular cells in health and disease. Nat. Rev. Immunol. 15, 350–361 (2015).
27. Fauci, A.S., Pantaleo, G., Stanley, S., Weissman, D.: Immunopathogenic mechanisms of HIV infection. Ann. Intern. Med. 124, 654–663 (1996).
28. Lundgren, J.D., Babiker, A., Gordin, F., Emery, S., Grund, B., Sharma, S., Avihingsanon, A., Cooper, D.A., Fätkenheuer, G., Llibre, J.M., Molina, J.-M., Munderi, P., Schechter, M., Wood, R., Klingman, K.L., Collins, S., Lane, H.C., Phillips, A.N., Neaton, J.D.: Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N. Engl. J. Med. 373, 795–807 (2015).

29. Maggiolo, F., Airoldi, M., Callegaro, A., Martinelli, C., Dolara, A., Bini, T., Gregis, G., Quinzan, G., Ripamonti, D., Ravasio, V., Suter, F.: CD4 cell-guided scheduled treatment interruptions in HIV-infected patients with sustained immunologic response to HAART. AIDS. 23, 799–807 (2009).
30. Perrin, D., Bezbradica, M., Crane, M., Ruskin, H.J., Duhamel, C.: High-Performance Computing for Data Analytics. 2012 IEEE/ACM 16th Int. Symp. Distrib. Simul. Real Time Appl. 234–242 (2012).