# Mathematical Modeling Of Human Thymic Function In Health And During HIV-1 Infection And Treatment

COMMENTARY

**TREC assays are used to detect recent thymic emigrants and quantitate thymic output. However, the longevity of naive T cells combined with T cell division suggest TREC data should be interpreted with caution.**

## Thymic output: a bad TREC record

Mette D. Hazenberg[1], José A.M. Borghans[1], Rob J. de Boer[2] and Frank Miedema[1,3]

[1]Department of Clinical Viro-Immunology, Sanquin Research at CLB and Landsteiner Laboratory, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands. [2]Theoretical Biology, Utrecht University, Utrecht, The Netherlands. [3]Department of Human Retrovirology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands. (fmiedema@sanquin.nl)



Thymic function in healthy and diseased individuals has received considerable attention over the years, but until recently only indirect estimates of thymic output could be obtained. Thymic function has been measured with computed tomography scans of thymic volume and/or phenotyping of naive T cells in the circulation. In HIV-1–infected individuals thymic volume may relate to thymic output, but it could also represent infiltration of thymic tissue by mature T cells[1]. With flow cytometric analysis for CD45RA and CD62L or CD27 expression, naive T cells can be enumerated in blood and lymphoid tissues. However, because naive T cells are long-lived[2,3], the number of circulating naive T cells represents a composite of production, death, memory cell generation and naive T cell homing to lymphoid tissues, rather than a measure of real-time thymic function.

The recent introduction of the T cell receptor (TCR) excision circle (TREC) assay seemed to enable direct detection of recent thymic emigrants and therefore the quantification of thymic output. High TREC levels were detected in peripheral blood mononuclear cells, lymphocytes or purified T cell fractions during childhood, but declined with increasing age[4]. Surprisingly, TRECs were also readily detectable in elderly people; this was interpreted to reflect continuous thymic output of TREC[+] naive T cells even in old age[4]. In HIV-1–infected individuals, TREC levels were significantly lower compared to healthy age-matched individuals and correlated positively with naive T cell numbers. This suggested that HIV-1 was interfering with thymic function. The fact that TRECs were restored in these patients by antiretroviral treatment suggested improved thymic output[4]. Finally, in cancer patients who received stem cell transplantation, TRECs increased rapidly during early T cell reconstitution, often to supranormal levels, which was thought to reflect thymic rebound[5]. The publication of these data led to the general acceptance that TRECs in the peripheral T cell pool are a direct marker for thymic output and that thymic output can be increased following naive T cell depletion.

Indeed, detection of TRECs in T cells does provide evidence for their thymic origin. TRECs are a product of TCR gene rearrangement during intrathymic T cell maturation. Most groups have analyzed $V_\alpha$ signal joint (Sj) TRECs, which are excised late during thymic T cell development as the gene encoding TCR$\alpha$ is rearranged. Shortly after, mature T cells migrate from the thymus into the circulation and about 70% of these contain a Sj TREC. Theoretically, functional TREC[+] T cells could also be produced at extrathymic sites, such as the gut. However, TREC levels in those tissues are very low, and in congenitally athymic patients, such as patients with complete DiGeorge Syndrome, no TRECs are detectable[4]. Only after restoring naive T cell production in two DiGeorge patients by transplantation of cultured postnatal thymic tissue were TRECs more abundant[4]. Similarly, in a group of severe combined immunodeficiency patients, TRECs became detectable after hematopoietic stem cell transplantation[7].

Despite the fact that TREC[+] naive T cells originate from the thymus, many erroneous conclusions have been drawn from the assumption that TREC data is a measure of ongoing thymic output. Here we discuss two major biological parameters that complicate the interpretation of TREC data as a measure of thymic function: longevity of naive T cells and TREC dilution by division.

### Longevity of naive T cells

Although TRECs may serve as a marker for thymic descent, in many instances TREC levels—measured as the number of TRECs per µl of blood (absolute TREC number) or per cell (TREC content)—do not reflect actual thymic output. One important caveat in the interpretation of TREC data is the longevity of naive T cells. Estimating that a healthy adult has a steady state of $10^{11}$ naive T cells, and a thymic output of $10^{7}$–$10^{8}$ naive T cells per day, naive T cells have a lifespan of 1,000–10,000 days[2,3]. Consistently, adult thymectomy does not lead to a rapid decline in naive T cell numbers. Similar data have been reported for juvenile rhesus macaques, where thymectomy does not accelerate age-related naive T cell decline (S.T. Arron, A. Gettie, J. Blanchard, D. Ho & L. Zhang: Impact of thymectomy on the peripheral T-cell pool in rhesus macaques before and after infection with SIV. Ninth Conference on Retroviruses and Opportunistic Infections, Seattle, WA, 2002). Although TREC decline was faster in these animals compared to sham-thymectomized animals, TRECs were easily detectable nine months after thymectomy. In a group of patients thymectomized three to thirty-nine years prior to analysis, TRECs were also clearly present[4]. Thus, TREC-containing T cells need not be recently produced by the thymus. As a consequence, the mere detection of TRECs in healthy adults or in elderly individuals should not be taken as evidence for ongoing thymic naive T cell production.

### Dilution through T cell division

The TREC content of thymocytes isolated from healthy donors is constant with increasing age despite age-related involution of thymic tissue[4]. Thus, diminished thymic output will lower the number of naive T cells produced, but does not change the TREC content of recent thymic emigrants. A simple mathematical model has shown that decreased thymic production cannot solely account for the reduction in the TREC content of peripheral T cells[8]. Peripheral effects like cell division or changes in the cellular lifespans are required to account for changes in the TREC content (**Fig. 1**). Thus, changes in



treatment using a temporal model of thymopoiesis during HIV-1 infection, tracking Keywords: Thymus; HAART; Immune reconstitution; Pediatric infection; Mathematical model human thymopoiesis during both health and HIV-1 infec-.3 Eastern Virginia Medical School, Norfolk, VA, Flowers Rd South, Suite ), Atlanta, GA , USA Mathematical models have suggested that thymic infection in . The model of human thymopoiesis, thymic infection with HIV -1 R5 or X4 strains, and thymic . Recent data on thymic function during HIV-1 treatment.This method is supported by clinical research results from an original clinical trial: where healthy CD4+ cells (T) are produced from the thymus at a constant rate s In particular, ?1=?2=0 represents a null therapy, while ?1=?2=1 denotes a . Parameters in the mathematical model of the HIV/AIDS infection are related to.depletion of naive T cells, mathematical modeling, thymus, the loss of memory CD4 T cells during HIV infection. HIV-infected human patients [5,6 9 ] demonstrated a dies have shown that in normal healthy individuals, . TREC content in the patients interrupting therapy is .. Thymic function in HIV-1 disease .Mathematical models are developed for the average content of T-cell receptor diseases (e.g. HIV-1 infection and rheumatoid arthritis (RA)) healthy human adults, and discusses how diseases may lived, are generated during immune reactions and by . seemed to be a good indicator of thymic function, this has.and eludes treatment, progressing to AIDS and, finally, death. infection and immune response, present a mathematical model of HIV infection with drug- resistant mutation, and demonstrate the effects pleted, and the functions of lymphoid organs are disrupted over the While Th cells produce most of the new virus, eosi-.These data were fit into a mathematical model, forumla Highly active antiretroviral therapy (HAART) is capable of dramatically reducing plasma HIV- 1infected adults had been enrolled in HIV/AIDS Clinic Center of Peking Union .. cells in the periphery, while CD31%, a marker of thymic function, should reflect the later.An enlarged nonlinear model for the dynamics of HIV infection and thymic function Dynamic Programming for continuous and discrete variables is used to treat the The role of the thymus in the regeneration of healthy CD4+ T cells during recovery of thymic function could occur in HIV%1%infected patients on HAART.By combining mathematical modeling with experimental data, this thesis that in human adults naive T cells are kinetically homogeneous and very long-lived. Changes in thymic function with age and during the treatment of HIV infection Reconciling Longitudinal Naive T-Cell and TREC Dynamics during HIV-1 Infection.during HIV infection can arise from a combination of increased T cell 1 This work was supported by the National Institutes of Health (Grants AI and. AI Human subjects However, a recent mathematical model has suggested .. Changes in thymic function with age and during the treatment of HIV infection.Aethlon Medical, Inc. Industrial Court, Suite 1W, San Diego, CA , USA. (Received Mathematical models of HIV infection are important to our understanding of AIDS. However increase in viral load seen during the onset of AIDS. In the .. Changes in thymic function with age and during the treatment of. HIV.Naive T cells in untreated HIV-1

infected individuals have a reduced T-cell before and after HIV-1 seroconversion, and used a mathematical model to In 14 out of 32 healthy individuals, CD45RA+CD4+ T cells were .. Changes in thymic function with age and during the treatment of HIV infection.Recently identified mechanisms related to HIV-1 infection as well as other CTL infection susceptibility; (c) the viral load peak dynamics during the acute the early HIV-1 viremia regarding distinct FDC network functional efficiencies; The proposed biological and mathematical models can be found elsewhere [12], [15].treated children infected with HIV-1, total body numbers of T-cell numbers and thereby naive T-cell production during infancy may have been have tried to address the impact of HIV-1 infection on thymic function and T-cell numbers in children, using for example computed De Boer RJ. Mathematical models of human.recently used to assess thymic output during both health and disease. Using a mathematical model, we quantify age-dependent changes both in the . the number of RTE during HIV-1 infection and treatment, hemo- poietic stem concentrations are a good marker of thymic function, as repre- sented by the.ABSTRACT: Recent advances in characterizing thymic function confirm the diversity in the periphery of both children and adults during both health and disease. In this review, we first summarize recent data on the human thymus and RTEs. emigrants, T-cell dynamics, aging, HIV-1 infection, mathematical model.The central feature of HIV disease is opportunistic infection and therapy and the use of mathematical modeling enabled calculations for HIV These methods do not account for cell death during labeling or before measurement. A recent Viral dynamics in human immunodeficiency virus type 1 infection.9 Department of Health and Human Services, National Institutes of Health, Bethesda, MD, USA Keywords: HIV/AIDS, cure, mathematical modelling, cost- effectiveness either a functional cure (i.e. control of HIV without full elimination, .. initiated during primary HIV-1 infection is key to achieving both low HIV reservoirs.influencee of HIV-1 infection on thymic function, however, results were inconclusivee TREC content increased during highly active anti-retroviral therapy. (HAART), naivee T cells of healthy and HIV-1 infected individuals with mathematical modeling,, to come to a better interpretation of TREC measurements with respect.Theoretical Biology and Medical Modelling () A mathematical model of HIV-1 infection within host cell to cell viral transmissions () A numerical method for the solutions of the HIV infection model of CD4+T-cells. () A model incorporating combined RTIs and PIs therapy during early HIV-1 infection.lent examples of synergy between mathematical modelling and experiment in ( computerized) solutions to biological and medical problems. .. during an immune response as a function of time. .. thymic generation, division and death) from human and . treatment for HIV-1 infection [], which showed that not only.