Mathematical modeling of HIV infection: an overview

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Relevance

Human Immunodeficiency Virus (HIV) is one of the most infectious and dangerous viral agents which still remains a major public health challenge in the world.

Despite the fact that since the discovery of the etiological agent of AIDS — the human immunodeficiency virus (HIV), 35 years have passed, nevertheless, the problem of the spread of HIV infection, treatment and quality of life of people living with HIV remains actual.

According to UNAIDS for 2016, there are currently 36.7 million people living with HIV and about 2.1 million new infections were recorded in 2015.

Global HIV epidemic (2016)

36,7 million people are living with HIV
(30,8-40,9)

1,8 million
new infections
(1,6-2,1 million)

1,0 million
HIV-related deaths
occur annually
(0,83-1,2 million)

Source: UNAIDS/WHO estimates

The main distinguishing features of HIV

HIV attacks the immune system cells that have CD4 receptors at their surface, such as T-lymphocyte-helper cells, macrophages, dendritic cells, etc. As a result, the immune system is depleted and the tissues of the lymphoid organs are destroyed.

The persistence of latent (asymptomatic) infection is an important feature of the pathogenesis of HIV infection: constant presence of large reservoirs of latently infected cells is one of the main obstacles on the way to eradication of HIV infection.

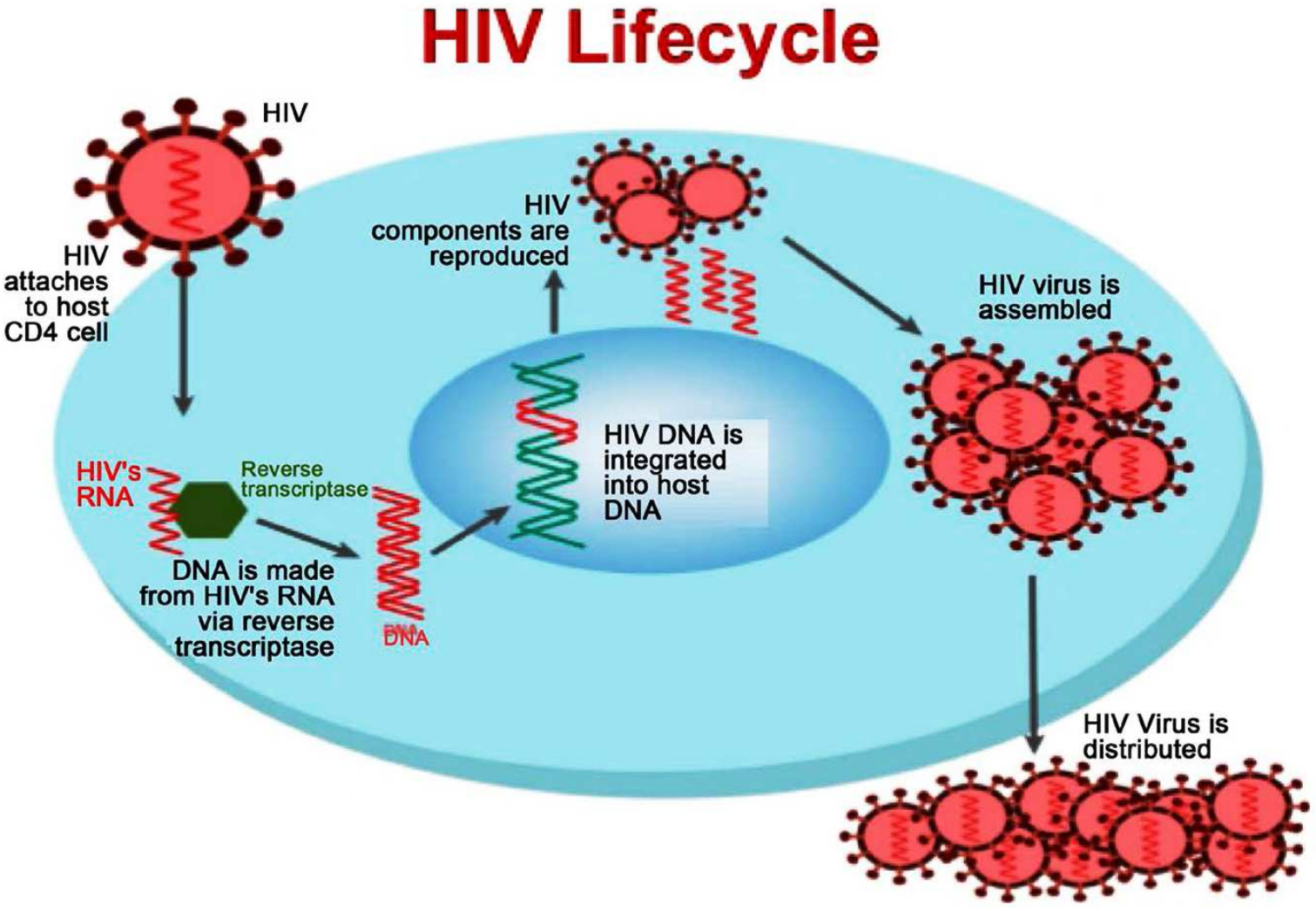
The main distinguishing features of HIV

HIV differs from other viruses by a high mutation level, the mutation rate is $10^{-5} - 10^{-4}$ per nucleotide during one replication cycle. In addition, since HIV belongs to the class of retroviruses, during the reverse transcription occurring at a high rate, multiple errors are produced and subsequently lead to emergence of new strains.

This allows the virus to "escape" from humoral and cellular defense factors of our immune system and to form multiplicity of drug-resistant strains.

Else more a paradoxical feature of HIV is that activation of the immune system does not lead to a suppression of virus multiplication, but to opposite to activation of latently infected cells, which start to produce new viral particles.

HIV life-cycle

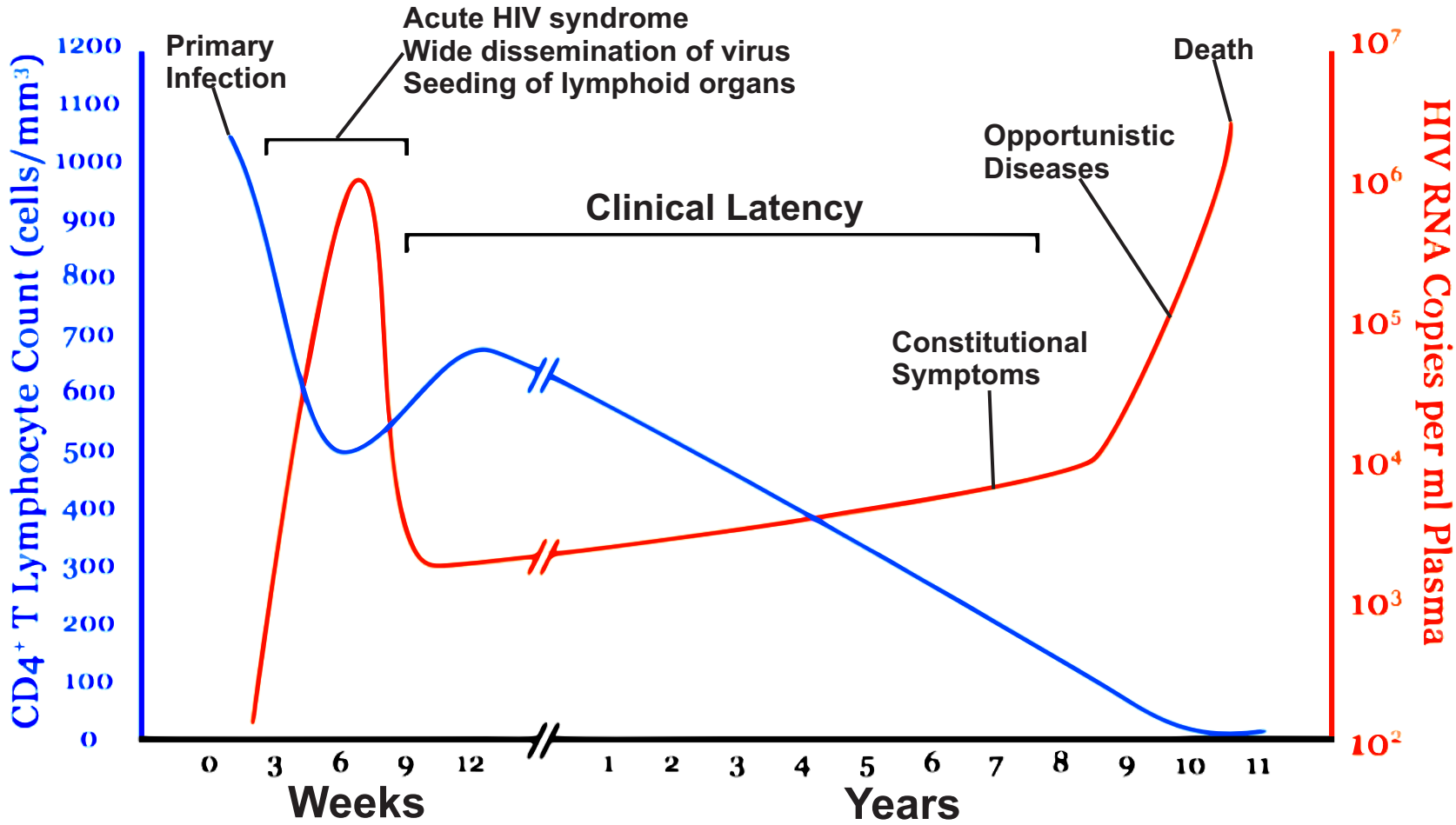


Source: McGilvray, M., and Willis, N., All about Antiretrovirals: A Nurse Training Programme, "Trainer's Manual," Africaid, 2004.

How HIV Works

1. HIV locates the CD4 cell and attaches to its surface. Having fused with the cell membrane, HIV releases its genetic material (viral RNA) and enzymes into the CD4 cell.
2. The enzyme reverse transcriptase copies the viral RNA into viral DNA.
3. The viral DNA is integrated in to the CD4 cell's nuclear material. This process is made possible by the enzyme integrase.
4. The individual components of HIV are then produced within the CD4 cell.
5. The individual components of HIV are then assembled together to make new HIV viruses. This process depends on the enzyme protease.
6. New viruses are released from the CD4 cell. These infect other CD4 cells where the cycle repeats itself.

Three phases of an HIV infection



Source: O'Brien, S., Hendrickson, S. Host genomic influences on HIV/AIDS, Genome Biology, (2013).

Highly active antiretroviral therapy (HAART)

Twenty years ago (1996-1997), the era of highly active antiretroviral therapy (HAART) began in the history of HIV infection. The introduction of treatment based on the use of a combination of antiviral drugs, has led to a significant improvement in the quality of life of patients, has caused a clear decrease in AIDS-related diseases and mortality.

At the present stage, the development of an optimal HAART strategy is impossible without the use of mathematical modeling methods and mathematical programming, due to a complex combinatorics of the drugs used and, as a result, the emergence of many drug-resistant strains. For example, a treatment scheme known as the mega-therapy (MDRT — multi-drug rescue therapy) may include combinations of 9 to 15 antiretroviral drugs.

The role of mathematical methods: Description, Interpretation, Prediction

The first mathematical model that describes the immune system response to HIV infection, appeared three years after the discovery of HIV, in 1986.

Cooper L.N. Theory of an immune system retrovirus (human immunodeficiency virus/acquired immune deficiency syndrome). Proc. Nati. Acad. Sci. USA (Medical Sciences), 1986.

Mathematical methods are used for:

- studies of the pathogenesis of HIV infection, testing theoretical hypotheses;
- studies of the immune response to HIV infection;
- predicting the course of HIV infection, its progression (acute phase, clinical asymptomatic phase, transition to the terminal stage – AIDS);

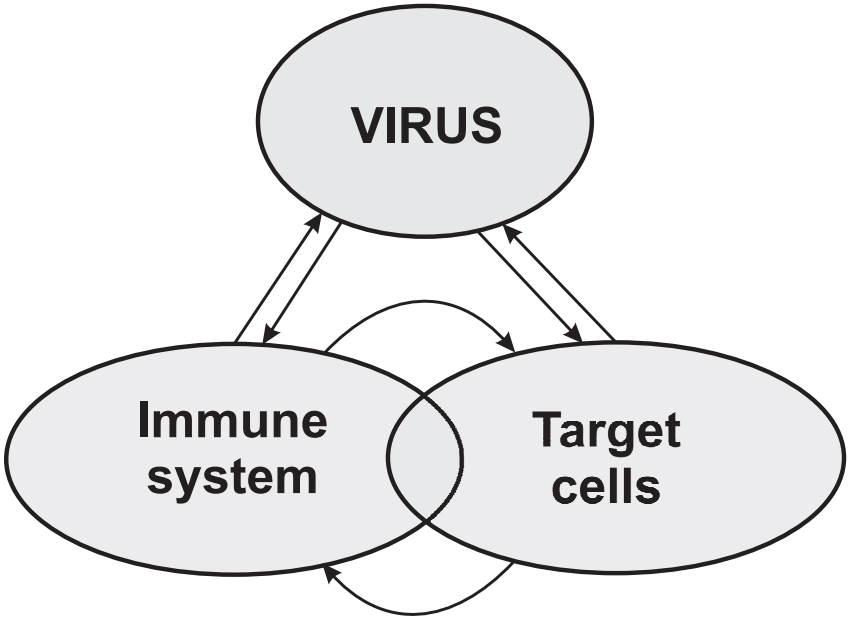
The role of mathematical methods: Description, Interpretation, Prediction

- development of personalized therapy that takes into account individual characteristics of a patient;
- development of complex combinatorial treatment schemes, studies of the joint action of drugs;
- assessing the toxicity of applied drugs for the patient;
- development and research of new treatment strategies;
- identification of unknown parameters that cannot be measured experimentally;
- processing and analysis of large data arrays: both recorded clinical cases and experimental data obtained using modern measurement methods (BIG DATA ANALYSIS);
- assessing the cost of treatment and making recommendations at the governmental levels to prevent the spread of the disease over the world.

The role of mathematical modelling and cost-effectiveness analysis in HIV clinical trials (SMART, STEP and others)

- Integrating multiple components of strategies: efficacy, toxicity, early and late relapse and cost
- Projecting long-term outcomes from short-term studies
- Evaluating more strategies than possible in a single clinical trial
- Assessing the impact in different target populations
- Evaluating the potential transmission benefits of cure
- Determining the cost-effectiveness, as well as affordability, of cure strategies compared to current antiretroviral therapy
- Assessing the value of information to be gained from proposed large-scale trials

Scheme of the "virus – host" interactions



VIRUS

Wild-type viruses
Drug-resistant strains
Drug-sensitive strains

IMMUNE SYSTEM

Dendritic cells, Macrophages, B-Lymphocytes
Memory cells, CD4+ effector cells
T-Lymphocytes, CD8+ cytotoxic cells
T-Lymphocytes and their precursors
Antibodies

TARGET CELLS

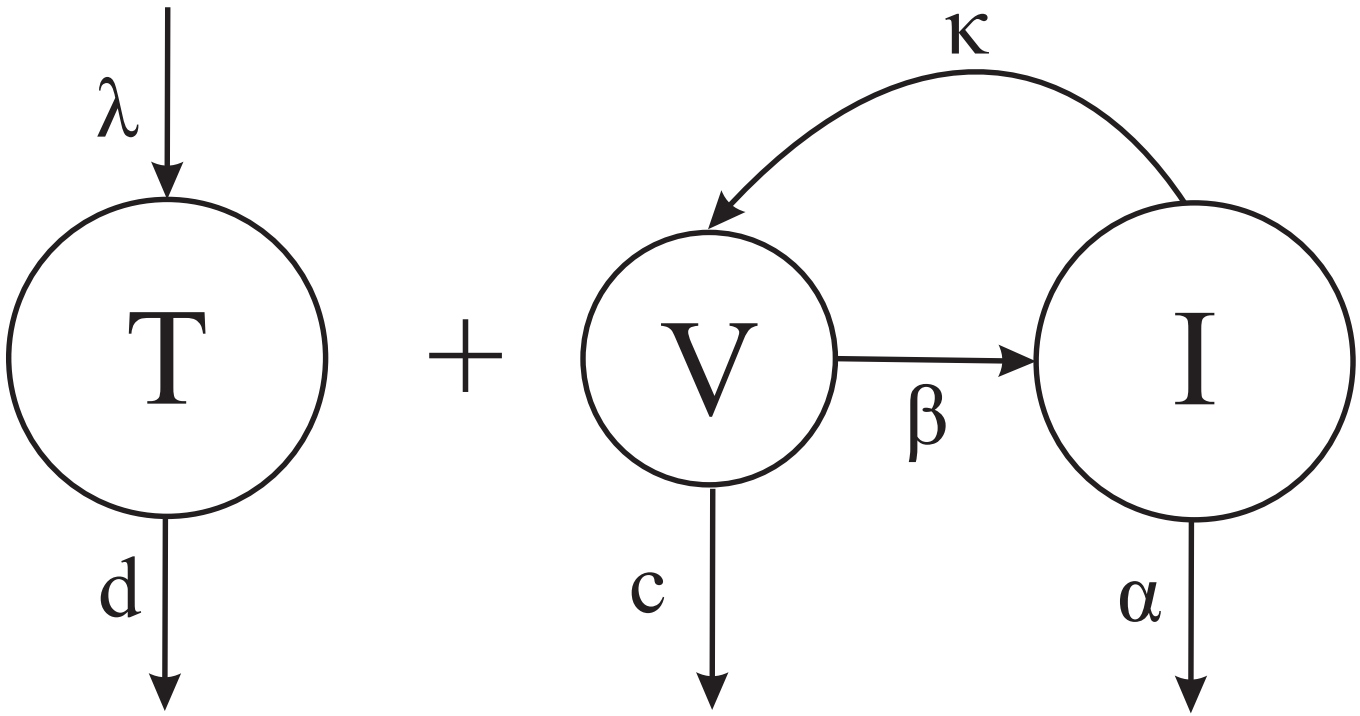
Type 1 T-helper and type 2 T-helper cells (CD4+ T-cells)
T-lymphocyte precursors in the bone marrow and thymus,
Monocytes, Macrophages, Eosinophils,
Dendritic cells, Microglia cells of the central nervous system

Details of existing frameworks for HIV infection modelling

Processess	**State space**	**Time scale**	**Math models**
Viral evolution	Wilde-type virus, mutants, viral genomes	Short-, long-term dynamics	Deterministic (ODEs, Integro-DEs, hPDEs); Stochastic (GA) algorithms
Virus-target cell dynamics	Viral load, uninfected- and infected- target cells (naive, memory; productively- and latently infected, CD4 T cells, APCs)	Short-term dynamics	Deterministic (ODEs); Stochastic (DEs)
Immune responses	CTLs, CD4 T cells, DCs, NK cells, APCs	Short-term dynamics	Deterministic (ODEs); Stochastic (DEs)
Whole infection: from primary phase to AIDS	Virus, CD4 T cell, CTLs, B cells, macrophages	Long-term dynamics	Deterministic (ODEs, hPDEs); Stochastic (agent-based, hybrid) models, DEs

The basic model of HIV infection

The basic mathematical model of the dynamics of HIV infection includes three key cell populations: uninfected target cells, infected target cells, and free virus particles.



The basic model of HIV infection

$$
\begin{aligned}
\frac{d}{dt}T(t) &= \lambda + dT(t) - \beta V(t)T(t) \\
\frac{d}{dt}I(t) &= \beta V(t)T(t) - \alpha I(t) \\
\frac{d}{dt}V(t) &= \kappa I(t) - cV(t)
\end{aligned}
$$

Susceptible target cells (T), infected cells (I) and free viruses (V) with differential equations. Target cells constantly enter the system at rate λ. These cells die at a natural death rate d and become infected at rate β. Upon infection, cells move into the I class and have a potentially increased death rate α. Infected cells produce viruses at rate κ. Viruses are removed from the system at rate c.

Basic mathematical model

This basic model allowed to obtain such important quantitative characteristics of the infectious disease as the virus replication rate and an average half-life of a virus particle, the rate of decrease of the viral load, a life span of infected T-lymphocytes and the rate of virus production by a single infected cell (basic reproduction number, R_0).

Basic reproduction number, R_0 is defined as the number of newly infected cells that arise from any one infected cell when almost all cells are uninfected.

$$R_0 = \frac{\beta\lambda\kappa}{\alpha dc}$$

Basic mathematical model

The next generation of dynamic models is an extension of the base model by considering various types of cells in the immune system, types of infection (acute, latent), localization in the compartments (blood, lymphatic system), mutated strains of the virus, etc.

$$
\begin{aligned}
dT_i/dt &= b_i(T_i, I_{ij}) - d_{T_i}(T_i) - \beta(T_i, V_j, I_{ij}) - S_T(I_{ij}, V_j, T_i) \\
dI_{ij}/dt &= \beta(T_i, V_j, I_{ij}) - d_{I_{ij}}(I_{ij}) - S_I(I_{ij}, V_j, T_i) \\
dV_j/dt &= \kappa(I_{ij}, V_j) - c(V_j, T_i, Y_j)
\end{aligned}
$$

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Thank you for your attention!