

# Human Immunodeficiency Virus Infection: from Biological Observations to Mechanistic Mathematical Modelling

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**Abstract.** HIV infection is multi-faceted and a multi-step process. The virus-induced pathogenic mechanisms are manifold and mediated through a range of positive and negative feedback regulations of immune and physiological processes engaged in virus-host interactions. The fundamental questions towards understanding the pathogenesis of HIV infection are now shifting to ‘dynamic’ categories: (i) why is the HIV-immune response equilibrium finally disrupted? (ii) can one modify the dynamic equilibrium for host benefit? (iii) can one predict the outcome of a system perturbation via antiviral drugs or drugs modulating the host immune response dynamics? Answering these questions requires a major interdisciplinary effort, and in particular, the development of novel mathematical approaches for a coherent quantitative description and prediction of intra-patient HIV evolution, the immunological responses to HIV infection, and the systems level homeostatic regulation of specific effector and regulatory lymphocyte populations in correlation with disease status. Here we summarized fundamental biological features of HIV infection and current mathematical modelling attempts to understand HIV pathogenesis.

**Keywords and phrases:** mathematical modelling, host–pathogen interaction, immune system, human immunodeficiency virus infection

**Mathematics Subject Classification:** 35Q92, 37N25, 92-02, 92B05, 92C30, 92C42, 93A30, 97M60

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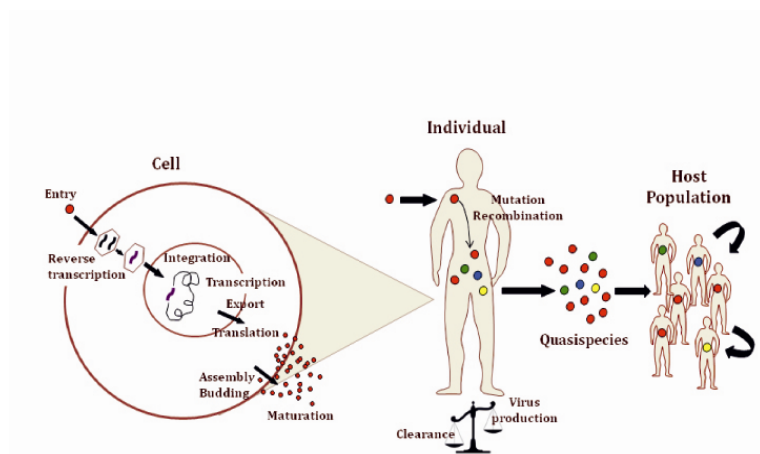
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## 1. Introduction

It has been almost 30 years since the discovery of the Human Immunodeficiency Virus (HIV) as the causative agent of AIDS [20, 78, 138, 153, 196]. Today, the HIV/AIDS pandemic affects about 35 million people worldwide, with an estimated 2.7 million new infections and 1.8 million AIDS-related deaths only in the year 2010 [263]. Even with the successful suppression of the virus by current Highly Active Antiretroviral Therapy (HAART) [9], the infection cannot be cured. Moreover, there is no effective vaccine available [146]. Reasons for these caveats are directly associated with two essential features of HIV. First, the HIV provirus can become latent in the target cell and therefore remain undetected by the immune response [75, 233] and current drug regimen. Second, the high intra-host diversity of HIV can drive the emergence of drug resistance [9] and reduce immune recognition [91, 252].

With the advent of new research tools our understanding of the HIV–host interaction has grown enormously in the last years. High-throughput screening (HTS) campaigns using siRNA have led to the identification of host factors either supporting or restricting HIV replication, thus opening the door for new therapeutic options [32, 39, 126, 139, 181, 200, 268, 274]. In particular, current research efforts are focused on depleting the latent HIV reservoir [54]. It has been proposed that crucial host transcription factors, such as NF- $\kappa$ B and NFAT, can be agonistically targeted to reactivate HIV from latency, thus allowing stimulated cytolytic T lymphocytes (CTL) to kill off infected cells [222]. Similarly, uncoiling HIV proviral DNA by targeting histone deacetylases (HDACs) and histone methyltransferases (HMTIs) has also been proven effective in reactivating the virus from latency [31, 163]. Furthermore, there is increasing evidence that HIV requires components of the cellular kinase signalling pathways for its replication, providing further options for the development of new antiviral strategies in the near future [158, 200, 229].



**FIGURE 1. HIV biology at the level of an infected cell, an infected host organism and spreading within a host population.** The consequences of the events of HIV replication at the cellular level are reflected in the infected individual that in turn determines the outcome at the host population level.

Despite the impressive research advances of the last years, an integrative view and quantitative understanding of the mechanisms of HIV-induced pathogenesis has not been fully achieved. This is in part due to the “language barrier” and knowledge gaps between mathematical modellers, immunologists and clinical and basic virologists. To reduce these gaps, this review summarizes the basic features of HIV biology that may be considered for an implementation into explanatory models of virus-induced pathogenesis (see Figure 1). Models of HIV epidemiology (see i.e. [197]) represent a separate field of research and are not considered here. Interested readers may also look at two recent reviews on basic HIV biology from another perspective [71,136]. Subsequently, previous modelling attempts are described that analyse certain aspects of intra-patient HIV evolution, the immunological responses to HIV infection, and the homeostatic regulation of specific T lymphocyte populations in correlation with disease. Together this may contribute to joint research efforts addressing neglected areas of fundamental biological and disease-associated processes in HIV infection.

### 1.1. HIV infection at the level of a cell

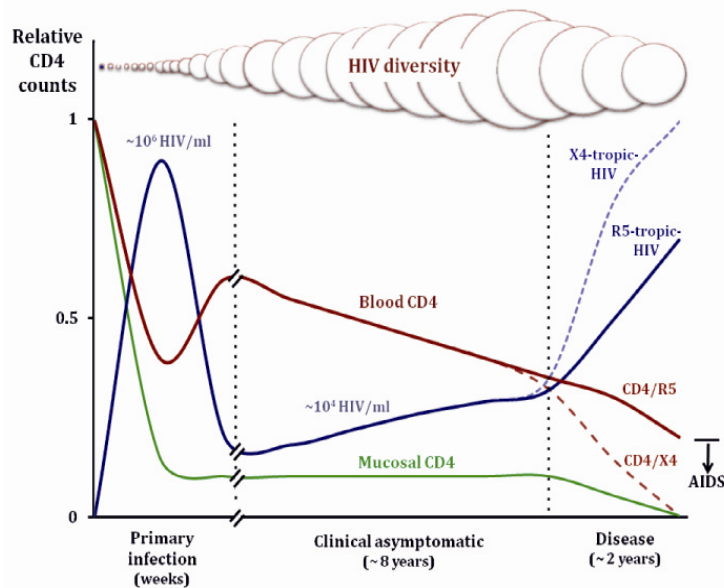
The cellular journey of HIV is a complex struggle between cellular defence mechanisms and viral-encoded counterparts [39,136,139]. HIV primarily infects CD4+ T cells and macrophages. Entry into a target cell is mediated by the interaction between the viral envelope, the cellular CD4 receptor, and the chemokine receptors CCR5 and/or CXCR4, which altogether determines the tropism of HIV. Once inside the cytoplasm, the viral-encoded reverse transcriptase (RT) catalyses the conversion of both single-stranded RNA genomes into one DNA molecule using deoxynucleotide triphosphates (dNTPs) as building blocks. The host restriction factor SAMHD1 can interfere at this step by downregulating intracellular dNTP levels [214]. Likewise, other retroviral restriction factors act at this early infection stage to dampen down virus expansion. These are TRIM5 $\alpha$ , that recognises retroviral cores and mediate their structural disintegration, and APOBEC 3 proteins that deaminate cytidines in single-stranded viral DNA regions with the consequence of DNA degradation or hypermutation [109,148,159,164,245,253,272]. To overcome host restriction, HIV has developed counterparts like Vif and Vpu that interact with the restriction factors and target them to proteasomal degradation [121,147,179,180,225,250].

Reverse transcription is the step within the viral life cycle in which point mutations and recombination events occur [127,152,162,184,202]. These are together with APOBEC-mediated hypermutation the main mechanisms in generating virus diversity. Subsequently, the HIV DNA is trafficked to the nucleus and integrated into the host chromosome with the help of the viral integrase. This HIV provirus may remain silent as a so-called latent provirus or use the cellular transcription and translation machinery to produce viral mRNAs and proteins that assemble to progeny virions at the cell surface. Infection of new target cells may then occur via cell-free virus or by cell-to-cell transfer through actin structures named virological synapses [212]. These late stages of the virus life cycle are utilizing the cellular transport machinery by means of the endosomal sorting complex (ESCRT) [22] and can be inhibited by the restriction factor BST-2/Tetherin [179,180,250]. Again as mentioned above, HIV has acquired a counterpart in form of the Vpu protein that interacts with the restriction factor and targets it to proteasomal degradation.

### 1.2. HIV infection at the level of a host organism

Already the events during primary HIV infection of a human set the stage for the following dynamic interaction between the virus and immune-physiological responses of the host that dictates the course of the infection (reviewed in [29,42,168,231]; see Figure 2 for main infection characteristics). In about 80% of cases, initiation of the infection is a clonal event [116,134]. The transmitted virus grows exponentially which in turn induces strong innate and adaptive immune responses including acute phase proteins [144], the cytokine cascade [133,204,239], B cell [151,248] and T cell responses [89,244]. This is associated with a significant depletion of the CD4 T cell pool. The depletion is most profound and irreversible in the gut-associated lymphoid tissue [34,51,154,187,199]. An explanation may be the observed ability of the envelope gp120 protein of transmitted founder virus to interact with the gut mucosal homing receptor  $\alpha 4\beta 7$  on mucosal CD4 T cells [8,176]. Associated with the destruction of the gastrointestinal

lymphoid tissue, the translocation of bacterial products like lipopolysaccharides (LPS) provides a stimulus to systemic immune activation thus fueling new bursts of productive virus infections, T cell proliferation and death [97, 101].



**FIGURE 2. Typical course of an HIV infection.** HIV infection has been classically divided into 3 stages based on viral load in plasma, decline of CD4+ T cells and clinical symptoms. The primary infection lasts a few weeks and is characterized by high peaks in viral load in the blood (viremia) and a fast decline in CD4+ T cell counts. After this acute phase of infection, the CD4+ T cell counts in blood partially recover and viremia decreases however the mucosal CD4+ T cell numbers remain low. During the long lasting clinical asymptomatic phase there is an apparent equilibrium between CD4 counts and viremia. Continuous virus replication then leads to the continuous destruction of the CD4+ T cell pool and progression of immunodeficiency. The final disease phase (= AIDS) is defined by CD4+ T cell counts lower than  $200/\mu\text{l}$  blood and is characterized by the appearance of opportunistic infections that ultimately lead to death of the infected individual when not appropriately treated by antiretroviral therapy. In about 50% of HIV-infected individuals, a co-receptor switch (from CCR5 to CXCR4, solid and dashed lines, respectively) of the virus is observed that is associated with a faster decline in CD4+ T cell counts. During the infection course, HIV diversity and complexity is mostly increasing but reduces towards the end (circles, see text for details).

The peak of HIV viremia is limited primarily by virus-specific CD8-positive T lymphocytes [89, 244]. Depending on the nature of the founder virus and the strength of the CTL response, the virus load decreases and stabilises at some level known as the viral set point [168]. This set-point is highly variable amongst infected individuals and is, together with chronic immune activation, a predictor of disease progression [86, 170, 171, 238]. A low virus set point correlates with a reduced decline in peripheral blood CD4 T cells and a longer time of the chronic infection phase until the onset of AIDS. In parallel to disease progression, a functional exhaustion of HIV-specific CTL has been observed [19, 62, 262, 267]. This immune dysfunction has the straightforward consequence of reducing virus control. Without antiretroviral

treatment, the HIV load slowly increases until the final AIDS stage at which the number of CD4 T cells have dropped below a critical level that is required for a proper functioning of the immune system.

A fundamental feature of HIV is error-prone replication together with its ability to multiply infect single cells. As a consequence the clonal infecting founder virus rapidly accumulates genetic mutations by point mutations and recombinations, and generates a mutant spectrum collectively called “HIV quasispecies” [88, 172]. The evolution of the viral quasispecies is determined by the mutation processes as well as by fitness-based selection and random sampling (see accompanying review of Domingo and Perales). Mutations in regions of HIV proteins that are recognized by HIV-specific CTL confer a selective advantage over un-mutated virus resulting from a decrease in elimination [168]. However this may be at the cost of a reduction in the efficacy of mutated virus replication. Experimental analysis of HIV quasispecies evolution over time revealed a linear increase of both, the viral divergence from the founder virus and the diversity within the quasispecies in the initial infection phase [223]. Subsequently the divergence stabilizes and the diversity declines questioning the genetic diversity of HIV to be the key factor for disease progression.

Despite considerable progress in the characterization of HIV host interactions (Table 1a and 2), several fundamental questions with respect to HIV pathogenesis remain unsolved. Why does the immune system fail to regenerate the depleted CD4 T cell compartment? Why is the apparent equilibrium of the HIV immune response finally disrupted? From the comparison of patient groups with varying disease progression rates and studies on progressive and non-progressive infection of immunodeficiency viruses of non-human primate animal models, several pathogenesis concepts have evolved: (i) chronic immune activation, (ii) depletion of mucosal CD4-positive memory T cells and (iii) CD4 central memory T cell population failure [97, 99, 101]. Resolving these and other pathogenesis issues as mentioned in Table 1b will require a major interdisciplinary effort, in particular the development of novel mathematical modelling approaches that are consistent with the complexity of the HIV host interaction and are able to integrate recent large-scale data sets derived from systems biology studies in humans and animal models [30, 73, 125, 149, 157, 206].

### 1.3. HIV at the host population level

Major initial steps towards prevention of HIV spread in humans were the recognition of how the virus is transmitted and the establishment of diagnostic serological tests (Table 1a). The era of antiretroviral therapy (ART) then started in the late 80’s with the introduction of the first drugs specifically targeting viral enzymes [9]. ART has proven effective in reducing HIV spread including vertical transmission, and has been proposed for pre-exposure prophylaxis [1, 92, 102]. After the observation that circumcised men exhibit a lower risk of becoming infected [166], circumcision is now considered as an important prevention tool.

The development of a successful vaccine, both for the prevention of a HIV infection or as an immunotherapeutic tool in the context of an already existing infection, has remained elusive. Early vaccine trials failed to generate neutralizing antibodies against strains other than the ones used to produce the vaccines and showed no evidence for protection [128, 167]. The subsequent STEP trial has even provided evidence for enhanced HIV susceptibility [38]. However, the recent RV144 trial in Thailand reported a mild 30% of protection [201] raising hopes that protection is achievable. In this context, ongoing studies with elite controllers and long-term nonprogressors might provide further clues of how to produce new and more effective vaccines [23, 72].

## 2. Mathematical models of HIV infection

In addition to hypothesis-driven human clinical trials, some insights into the pathophysiology of HIV infection are gained using modelling approaches including the *in vitro* culture systems, the *in vivo* animal models (humanized mouse-, transgenic rodent-, non-human primate models) and mathematical models [242]. To handle the analysis of immunological, virological and physiological processes underlying the variation between individuals in the dynamics of acute and chronic phases of HIV infection in

an integrated manner, a major interdisciplinary effort is required, and in particular, the development of novel mathematical approaches for a coherent description and quantitative, dynamic analysis of an intra-patient HIV evolution and the immuno–physiological responses. Obtaining a quantitatively correct and predictive mathematical model of HIV infection that will provide accurate estimates of the scale of events is a challenge that has not been routinely implemented in many efforts at modelling of HIV infection. The mathematical models developed so far to address various aspects of HIV infection (see Table 3) can be subdivided into descriptive–, explanatory– and predictive ones. In general, the model equations are formulated by putting together elementary functional forms (building blocks) for the growth, death, differentiation, etc. processes rather than by deriving constitutive equations from the first principles of physics (e.g. conservation of mass and energy). Typically, researchers borrow concepts from ecology, enzyme kinetics or epidemiology, making use of the mass action law to formulate equations and describe the dynamics by systems of ordinary differential equations (ODEs). We review representative modelling frameworks, which have been proven to be instrumental in enabling greater insight into quantitative parameters of virus–host interaction and the kinetic determinants of disease progression.

## 2.1. Elementary models

The broadly used (so called ‘generalized consensus’) basic model of HIV infection (see for further details [189]) describes the population dynamics of target cells (CD4 T cells, macrophages, dendritic cells) —  $T(t)$ , productively infected cells —  $I(t)$ , and free virus —  $V(t)$ . The equations of the above T-I-V type model which consider the target cell production in thymus, their homeostatic proliferation at the periphery, virus infection, death and virus production, read as follows:

$$\begin{aligned} \frac{d}{dt} T(t) &= s + pT(t) \left( 1 - \frac{T(t)}{T_{max}} \right) - d_T T(t) - kV(t)T(t), \\ \frac{d}{dt} I(t) &= kV(t)T(t) - \delta I(t), \\ \frac{d}{dt} V(t) &= N\delta I(t) - cV(t). \end{aligned} \tag{2.1}$$

The set of equations can be further expanded to consider various types of heterogeneity in the HIV-immune system, e.g. types of infection (productive, latent), nature of target cells, virus escape mutations (see Table 4) [80, 182, 189, 254].

The above type of models for virus dynamics is seriously deficient as the immune response to HIV is not considered. The extended versions describe the population dynamics of immune, mostly the cytotoxic T lymphocyte response in a simple way using various functional forms which relate the proliferation term to the abundance of virus or target cells in the host [182]. The general form of the CTL dynamics —  $E(t)$ , which considers cell production in the thymus, their normal death, HIV-induced proliferation and impairment of immune responses observed in HIV infection, can be specified as follows (see for the details [2]):

$$\frac{d}{dt} E(t) = \lambda_E - d_E E(t) + \{f_{div}(V, I, T, p_{div})E(t) - f_{imp}(V, I, T, p_{imp})E(t)\}. \tag{2.2}$$

The model can be further expanded to take into account different CTL states (naïve, memory, anergic, effector, etc.) and types of regulations underlying the transitions between the states [208]. The combination of virus and immune response dynamics (modules (2.1) and (2.2)) with proper modification of the infected target cell equation to account for the CTL-mediated elimination provides a tool to qualitatively explore the impact of various parameters of virus–host interaction and antiviral treatment regimes on HIV infection dynamics [2]. Note that the parameterization of the dependence of immune responses on HIV infection characteristics deserves further attention as their long–term regulation in the chronic phase is poorly understood.

## 2.2. Short-term descriptions of HIV infection

High viral load and severe loss of CD4 T cells in mucosal compartments are a hallmark of acute HIV infection (see Figure 2). The course of acute infection is determined by the development of innate and then adaptive immune responses. Activation of the host immune system is considered to be a key factor of the pathogenesis of HIV infection (see Table 1b).

### 2.2.1. Innate immune responses

Dendritic cells (DC) and natural killer cells (NK) are the principal mediators of innate immune responses. DCs can both induce the antiviral adaptive response and promote the spread of the virus. There are few mathematical models that were developed to examine the above duality issue. An ODE based model developed in [119] considered the population dynamics of cell–virus interactions for CD4 T cell, CD8 T cells, DCs and HIV. The immune cells were further subdivided into subsets representing different activation/maturation states. The parameters were assessed from published sources. Sensitivity analysis was used to evaluate the effect of particular interactions and depletion of specific cell populations. A more detailed quantitative model of the initial inflammatory response to HIV invasion has recently been published [261]. It considers the population dynamics of 17 subsets of immune cells, including DCs, helper CD4 T cells and regulatory CD4 T cells. The model is formulated with ODEs and takes into account the birth/death-, contact/interaction and migration processes. The parameters of the model were quantified using elaborate procedures based upon sensitivity analysis and ordinary least squares fitting. This calibrated and validated inflammatory response model can be further used as an “elementary” building module for setting up multi–scale mathematical descriptions of HIV.

### 2.2.2. Adaptive immune response

A first quantitative modelling of the adaptive immune response in the primary HIV infection using patient’s data was implemented in [240]. The authors used a phenomenological description of the impact of CTL response parameterized via viral load on the elimination rate of the infected cells. The parameters of the model were estimated using the log-least squares distance criterion and clinical data covering the time range of up to 500 days post infection. The mathematical description of the CTL response was further refined in [49]. To this end the authors extended the model by equation for the rate of change of the CTL population in which the birth term was assumed to be linearly dependent on the abundance of target cells. A time delay between the infection and appearance of the differentiated effector cells was taken into account. The ODE and DDE versions of the model were compared by analyzing the consistency with the clinical data of the corresponding best-fit solutions. Different functional forms to model the regulation of CTL responses were examined in [49]. In particular, the authors assumed a bounded rate function of the number of infected cells in the proliferation terms. The calibrated model was shown to reproduce diverse patterns of virus kinetics observed in primary HIV infection.

In addition to deterministic models, there exist few stochastic models of early HIV infection (Table 4). The model formulated with stochastic differential equations proposed in [132] is an extension of an ODE model of T-I-V type obtained by considering additive noise terms in the form of Wiener processes. A different stochastic approach utilizing the branching–process framework to model the interaction between the virus, target cells of monocyte type and T cells can be found in [264]. The stochastic models are particularly suitable to analyze extinction events in the context of immune or antiviral interventions.

### 2.2.3. Chronic infection

Following the acute infection phase, virus level declines to a set point thus establishing a chronic phase of infection which can be interpreted as a quasi–steady state of the virus–host system (see Figure 2). The mathematical models for the chronic phase HIV infection developed so far are based upon the use of the same simple modules like the basic model of virus dynamics [182, 189]. Some important estimates of HIV infection parameters provided by fitting the models of the above family to clinical data were obtained in [175] (Table 2). The impact of escape from immune responses on viral load was estimated in [131]. A single escape event was shown to result in a viral load increase during the chronic phase by 10% to 50%.

However, only 6% of between-individual variation in viral load could be explained by the escape events. Using data from Los Alamos National Laboratory sequence repository and longitudinal studies, a simple exponential growth model for HIV was utilized to estimate the selective advantage of escape mutants, i.e. the relative rate of escape (see Table 2) [11].

Longitudinal clinical data sets, which are available for the chronic phase of HIV infection, are important for the validation of mathematical models. Instructive examples are presented in [3,17]. The predictive capability of the long-term models was assessed by comparing the model simulations with parameters estimated from half of the longitudinal data sets to full data sets. The so calibrated models were further used to explore treatment strategies via optimal control methods [4,18,61,205].

### 2.3. Long-term descriptions of HIV infection

To describe the long-term course of HIV infection from the initial acute infection phase through chronic persistence to AIDS, the basic model of virus replication is used being supplemented by the equations that simulate the immune response and, importantly, reflect specific hypothesis regarding the impairment of the homeostatic regulation of T cell populations in lymphoid tissues and blood. The corresponding parameterizations of the functional forms can be rather elaborate however they have in common that they use time-dependent or resource-dependent factors that introduce instability of the quasi steady state.

One of the first models to describe the whole HIV infection course in terms of T cell counts rather than viral load was proposed in [120]. The model structure reflects the assumptions about two feedback loops, one coming from the CTL mediated destruction of HIV infected CD4 T cells (negative feedback) and the other takes into account the dependence of CTL proliferation on CD4 T cell abundance (positive feedback). The model structure was sufficiently rich to describe the data on kinetics of CD4 and CD8 T lymphocytes over a seven year period.

Realistic modelling of HIV infection requires consideration of virus population dynamics which is regarded as a ‘moving target’ [237] for the immune system because of the emergence of virus mutants. The model proposed in [106,107] was used to predict the entire trajectory of the HIV infection spanning about ten years. The population dynamics of macrophages, CD4 T cells, wild type- and mutant virus, and CTLs was described using a combination of the T-I-V type (2.1) and E-type (2.2) basic models. In the corresponding equations the bounded rate forms for proliferation terms and bilinear interaction terms were considered. Remarkably, the model was calibrated by the clinical data for typical progressors and long-term non-progressors. The model was further extended by considering the pharmacokinetic module in order to explore the options for patient-specific treatment with three antiretroviral drugs (RDV, 3TC, ZDV). Overall, the study provided the list of kinetic model parameters for a comparative analysis of rapid- versus typical progressors and long-term non-progressors [107]. The specified values confirm the point stated in [175] that variations in multiple parameters can (and are enough to) account for large variations in HIV dynamics. A bifurcation analysis of the simplified version of the model proposed in [106] was further applied in [117] to reveal a subset of parameters which may produce two distinct types of steady states: a stable one, corresponding to individuals who do not develop AIDS and the second, unstable one, representing patients who develop AIDS in about 10 years.

A simple quantitative mathematical model to describe the long-term kinetics of HIV infection with a focus on the effect of immune activation, the key element of HIV pathogenesis, on CD4 and CD8 T cell populations and on the maintenance of infection through the activation of infected resting memory T cells was proposed in [40]. The immune activation was assumed to induce programmed cell death in T lymphocytes, which was parameterized via bi-linear functions of the number of activated infected T cells. The parameters of the model were estimated via least squares function minimization using some published clinical data on T cells and viral load dynamics. The biological consistency of the model was further examined via bifurcation and the sensitivity analysis of the solution. The analyses revealed the increasing correlation between apoptosis and infection-immune response parameters with the time of infection.



A detailed mathematical model for the host’s immune response to HIV infection was proposed in [259] to examine the sensitivity of the global infection dynamics to the model parameters. The model was calibrated to reproduce essential features of CD4 T cells and viral load dynamics, including the establishment of viral load set point, steady state and development of AIDS. The state space of the model (15 time-dependent variables) spanned CD4- and CD8 T lymphocytes subdivided into uninfected-infected, virus-specific and non-specific subsets, infected and uninfected macrophages, HIV-specific neutralizing antibodies and viral load. The decline of the thymic function with aging and the mutation-induced changes in the virus cell tropism were taken into account in the model. The functional forms for the processes considered in the model were specified using bilinear- and bounded rate functions. The study provides a rich analytical source of the estimates of virus-host interaction parameters (more than 35). It was shown that 10% variation of the model parameters is enough to mimic individual host differences in the dynamical patterns of HIV infection.

A hybrid computational model of HIV-1 infection has been proposed recently to study optimal therapy regimes [185]. The model is based on agent-based description of the interaction between the following populations: viruses, antibodies, macrophages, dendritic cells, CD4 T cells, CTLs, B lymphocytes and plasma cells. The virus population is represented as a set of two binary strings of length 16, corresponding to B-cell and T-cell epitopes, respectively. The Hamming distance is used to determine the affinity of the interaction. To take the spatial aspects of the interaction between the above entities into account, lymph nodes are represented as three-dimensional ellipsoid lattices with periodic boundary conditions. The spatio-temporal evolution of the concentration of small molecular weight molecules (interleukins and chemokines),  $c(t, x)$ , is described using the following type of reaction-diffusion equation with diffusion-, decay- and source terms on the right-hand side:

$$\frac{\partial}{\partial t} c(t, x) = D\nabla^2 c(t, x) - \lambda c(t, x) + s(t, x). \quad (2.3)$$

Finally, the model also includes the intracellular level of description by considering antigen digestion and presentation within a single cell. The parameters of the model were calibrated to describe a broad range of acute HIV infection dynamics, viral set points, the variation in the elapsed times between infection and the onset of AIDS as observed in rapid-, normal-progressors and long-term non-progressors, and the mutation-selection mediated evolution of virus tropism [185]. Overall, this is a first multi-scale computational model (implemented as C-ImmSim simulator) which enables the analysis of the long-term spatio-temporal aspects of HIV infection dynamics via a combination of discrete stochastic- and continuum deterministic descriptions integrating the single cell- and cell population levels of resolution.

The activation of CD4 T cells by HIV and pathogens unrelated to HIV is considered as an important component of HIV pathogenesis. A mathematical model to study the effect of multiple T cell responses to many different antigens over time on the long-term dynamics of HIV infection was proposed in [76]. The dynamics of exposure to and clearance of antigens are described by stochastic differential equations for the probabilities of T cell activation coupled to deterministic equations for CD4 T cells, CD8 T cells and viral load dynamics with the activation and infected cell heterogeneity taken into account.

## 2.4. Spatial representation of the immune system

Spatial heterogeneity is an essential feature of HIV-1 infection. Unfortunately, this type of heterogeneity is practically unexplored via mathematical modelling approaches. Lymphoid organs are the major compartments supporting virus replication. Using a compartmental model of virus exchange between the populations of free virus and the virus bound to follicular dendritic cells in lymphoid tissues, free virus in plasma and other tissues cells, it was shown that lymphoid tissues represent the major sink compartment of the body with the virion clearance rate of 50 to 500 per day [63]. A first explicit consideration of the lymph node (LN) network was proposed in an agent-based model of HIV infection [192]. The model considers as agents the viruses, CD4 T cells, CD8 T cells and antigen-presenting cells. The LN network, implemented as 2-dimensional matrices, allows one to account for accurate localization of cells relevant

for the cellular interactions as well as the circulation of immune cells between the nodes. The model was used to study the effect of the composition (e.g., the incorporation of gastrointestinal tract) of the network on the long-term progression of HIV infection.

## 2.5. Models of HIV quasispecies

HIV has enormous evolutionary potential so that the level of the genetic diversity of the HIV population changes in response to selection pressures. The specific issues that have been explored so far include the emergence of drug resistance and immune escape mutants, the effect of multiple target cell infections and recombination and the effective population size of the HIV replication–mutation processes. Mathematical models of the genetic evolution of HIV in the course of infection represent several approaches (Table 4).

One approach of HIV evolution modelling is based on the deterministic representation of the quasispecies theory [182]. It describes the population dynamics of growth-death of a set of virus mutants (vector  $\mathbf{v}(t)$ ), which differ in their replication rate (fitness) and mutation probabilities, with systems of ODEs of the following structure:

$$\frac{d}{dt} \mathbf{v}(t) = \mathbf{W}\mathbf{v}(t) - d(\mathbf{v}(t))\mathbf{v}(t). \quad (2.4)$$

Here, the matrix  $\mathbf{W}$  depends on replication and mutation parameters, and  $d(\cdot)$  parameterizes the decline due to finite life span and competition between the mutants. The deterministic quasispecies approach to analyze HIV evolution assumes that (is justified when) the population size ( $N$ ) is large enough, e.g.  $N \gg 4^L$ , where  $L$  is the nucleotide length of the viral genome,  $\sim 10^4$ . The above inequality ensures that the frequency of a given mutation at any given time is predictable. In HIV infection, although the total viral population size (census) is large ( $\sim 10^{12}$ ), the effective population size of HIV is much smaller. It is estimated using mathematical methods to be in the range of  $10^3 - 10^5$ , depending on the underlying assumptions [36, 142, 207]. The small effective size of the virus population increases the role of random sampling so that the evolution shifts from fitness based selection towards the stochastic mode of random sampling (drift). A thorough analysis of the transition between stochastic evolution and deterministic evolution modes is presented in [209]. The authors use (a) the forward Kolmogorov equation which describes the evolution of the probability density function  $\rho(t, f)$  of the mutant frequency ( $f$ ) under the effect of random drift ( $N$  — population size), selection ( $s$  — selection coefficient) and mutation ( $\mu$  — mutation rate) processes:

$$\frac{\partial}{\partial t} \rho(t, f) = \frac{f_{max}(1 - f_{max})}{2N} \frac{\partial^2}{\partial f^2} \rho(t, f) + s f_{max}(1 - f_{max}) \frac{\partial}{\partial f} \rho(t, f) + \mu(2f_{max} - 1) \frac{\partial}{\partial f} \rho(t, f) \quad (2.5)$$

and (b) the discrete evolution equation describing the probability  $p(t, n)$  of  $n$  mutants at time  $t$  as a Markovian process  $p(t + 1, n) = \sum_{n=0}^N P(n|n)p(t, n)$ , see [209] for details.

The models were used to predict the stochastic versus deterministic modes of viral evolution in relation to the replication–mutation parameters such as the mutation rate, selection coefficient, and the effective population size.

In addition to mutation and selection, multi-infection of susceptible cells and subsequent recombination contribute to the genetic diversification of HIV population in the course of infection. However, incorporation of multi-infection and recombination into deterministic continuous descriptions (based on ODEs) is technically extremely elaborate as one can see from [15]. Simplified scenarios were studied in [7, 66] using integro–differential equation versions of the basic virus dynamics model.

The deterministic model proposed in [150] extends the standard T-I-V type of virus replication description by the variables denoting the number of doubly infected cells. The extended model was used to study the effect of recombination on the emergence of drug resistant genomes with specified number (1 to 5) of mutations, called the genetic barrier of the drug. The number of distinct mutant genomes

considered in the model can be as large as 31, depending on the number of required mutations. However, the model ignores the existence of cells infected with more than two proviruses integrated into the cellular genome.

Genetic algorithms (GA) present a natural stochastic modelling tool to study the combined effect of mutation, recombination, selection and multi-infection [26,255]. To this end, the standard scheme of GA needs to be extended to take account of the multiplicity of target cell infection, which can range from 1 to 8 proviruses. The GA models implemented in [26,255] were used to simulate the genomic diversification of HIV within an infected individual and to study the effects of variation in the fitness between the mutants, recombination and proviral copy number on the emergence of multi-point mutations. The simulations considered the virtual genomes coded as  $2 \times 100$  bit strings and a population size of about 1000. The study supported the view that in finite size virus populations the evolution of the mutant spectrum can be purely neutral and that multi-infection/recombination can accelerate the emergence of multi-point mutants.

### 3. Conclusions

In the analysis of the pathogenesis of HIV infection the focus of research is on understanding the robustness and fragility of “. . . a persistent state of immune activation, characterized by multiple, recurrent bursts of lymphocyte proliferation, differentiation, migration, death and functional modification of ‘resting’ cells, is associated with progressive depletion of central memory CD4+ T cells, and ultimately, a collapse of effector site CD4+ memory populations that is closely associated with overt immune deficiency” [97]. The ability to resolve these issues in human studies is obviously limited. Mathematical modelling has proven to be an important research tool in immunology [95]. The overview of the existing approaches to the complexities of virus-host interaction in HIV infection clearly indicates the gaps that require attention of applied mathematicians (Table 3). Models of HIV infection have traditionally assumed spatially homogeneous virus populations, ignoring the metapopulation structure of the infection process [77] and neglected the kinetic heterogeneity in virus production due to localized bursts of HIV infection sustaining the continuity of the infection process [96,97]. HIV replication (ontogeny) in infected cells requires a much more detailed analysis to identify the most sensitive stages for control. Importantly, the architecture (geometry and stromal organization) of immune responses in lymphoid tissues, which is disintegrated in the course of HIV infection, needs to be considered in the mathematical models. Finally, the data on global gene expression and regulation at a single cell level in HIV infection provide a fundamental source of information for ever finer understanding of the pathogenesis of HIV infection via a systems biology approach. Such a multi-scale integration using novel computational modeling and identification techniques should enable one, given the complexity of HIV infection, to utilize the inherent precision of the mathematical language to clearly differentiate among alternative hypothesis of HIV pathogenesis [95].

Appendix

**Table 1a.** Important discoveries in HIV biology

Level	Event	Ref.
<b>Cell</b>	CD4 is the receptor for HIV	[60,138]
	CCR5 and CXCR4 are the main HIV co-receptors	[52,59,69,270]
	HIV env interacts with $\alpha 4\beta 7$ integrin of gut-homing lymphocytes	[8,48,256]
	HIV replicates in T cells and monocyte/macrophages	[44,58,85,123,143,218,220,228]
	Dendritic cells capture HIV and transmit it to T cells	[41,82,83,94,114,124,249,251,265]
	HIV life cycle is sensitive to intracellular dNTP levels	[156,173]
	Point mutations, recombination and hypermutation contribute to HIV diversity	[53,109,148,159,164,203,253,272]
	Cell-cell transmission is efficient in HIV spread	[165,193,198,210,212,227,232]
	HIV life cycle depends on multiple host factors	[32,39,126,139,181,200,268,274]
	Multiple host factors can restrict HIV	[121,147,179,180,224,225,245,250]
<b>Individual</b>	First description of an acquired immunodeficiency in young gay men	[90]
	First isolation of HIV-1 and genome sequencing	[20,258]
	First isolation of HIV-2 and genome sequencing	[50,103]
	HIV infection is a clonal event with $\alpha 4\beta 7+$ CD4+ T cells as key targets	[116,134,176]
	HIV-infected individuals carry a heterogeneous virus population referred to as a quasispecies	[5,88,108,172,266]
	HIV multi-infection of single cells	[35,129,130,219,235]
	Dynamic nature of HIV infection in vivo	[118,188,190,257,260]
	Viral set-point after primary infection and immune activation are predictors for disease progression	[86,170,171,238]
	Innate and adaptive immune responses after HIV infection	[6,84,89,135,168,174,215,236,239,247]
	HLA region polymorphisms in the host are major determinants for disease progression and control	[191]

**Table 1a.** Important discoveries in HIV biology (continued)

Level	Event	Ref.
<b>Individual</b>	HIV replication in and destruction of lymphoid organs	[70, 187, 199]
	Early depletion of mucosal CD4 T cells	[34, 51, 154, 169, 217]
	HIV latency in memory T cells	[47, 75, 188, 233]
	Exhausted T cell signature in chronic HIV infection	[19, 62, 262, 267]
	HAART blocks disease progression	[13, 137, 213, 241, 246]
<b>Host population</b>	Diagnostic test to detect HIV infection	[37, 211]
	HIV is transmitted by blood products, sexual contact and breast feeding	[25, 27, 64, 87, 105, 141, 155, 177, 221]
	ART reduces mother-child transmission	[102]
	HAART reduces HIV spread	[55, 67]
	Pre-exposure prophylaxis reduces HIV spread	[1, 92]
	Circumcision reduces HIV transmission	[14, 16, 28, 166]
	Vaccine-mediated enhancement of HIV spread (STEP trial)	[38]
First vaccine trial with evidence of low efficacy (RV144 trial)	[110, 201]	

**Table 1b.** Major conceptual developments in the understanding of HIV pathogenesis at the level of the individual

Event	Ref.
Clinical latency during the chronic phase of the disease does not correspond to latency of the virus	[186, 187, 257]
Immune activation is a major driving force of disease progression	[10, 24, 45, 65, 86, 98, 112, 216, 226, 234, 257]
Elevated lymphocyte turn-over in chronic infection is not a homeostatic response to cell loss	[56, 96, 99, 100, 111, 113]
Loss and/or dysfunction of central memory and naive cells rather than that of effector and effector-memory cells is a leading process in disease progression	[97, 98, 183, 195, 234]
The majority of latently-infected cells does not constitute a quiescent archive of virus but is a highly dynamic pool that is likely to be involved in driving the pathogenic process	[96, 140, 238, 243]
Bacterial translocation is a major driver of chronic immune activation	[33, 68]
Lymphoid tissue destruction is associated with chronic activation and disease progression	[104, 199, 271]

**Table 2.** Fundamental parameters of HIV infection

Parameter	Unit	Estimate [range]	Ref.
Total viral load	Virions in the lymphoid tissue (LT)	$10^{10}$ [ $7 \times 10^9, 10^{11}$ ]	[175]
Total number of CD4 (CD8) T cells in humans	Cells	$2 \times 10^{11}$ ( $10^{11}$ )	[79]
Abundance of lymphocytes in blood vs. LNs and spleen	Relative fraction	2.2% vs. 56.4%	[79]
CD4 T cell (CD8) level in normal vs. HIV-infected individuals	Cell / $\mu$ l	$1300 \pm 452$ vs. $432 \pm 241$ ( $618 \pm 257$ vs. $966 \pm 484$ )	[115]
Production rate of CD4 T cells (CD8) for blood in normal vs. HIV-1 infected individuals	Cell / $\mu$ l / day	$10.4 \pm 6.5$ vs. $9.0 \pm 4.8$ ( $5.9 \pm 7.6$ vs. $24.6 \pm 13.4$ )	[115]
Death rate of CD4 T cells (CD8) in normal vs. HIV-1 infected individuals	1 / day	$0.008 \pm 0.005$ vs. $0.029 \pm 0.013$ ( $0.009 \pm 0.013$ vs. $0.029 \pm 0.013$ )	[115]
Number of productively infected cells	Cells per LT (700 g) of the host (70 kg)	$10^8$ [ $10^8, 7 \times 10^8$ ]	[175]
Death rate of productively infected cells	1 / day	0.5 – 4	[175]
Clearance rate of free virus	1 / day	12 [2.2, 18]	[74]
Infection rate of target cells	1 / virion / day	$8.5 \times 10^{-11}$ [ $5 \times 10^{-12}, 10^{-10}$ ]	[175]
Rate of production of target cells	Cell / day	$2 \times 10^9$ [ $10^9, 7 \times 10^9$ ]	[175]
Selective advantage of escape (mutant) variant*	1 / day	0.001 – 0.5	[11]
Effective recombination rate	Recombination / base / generation	$\sim 10^{-5}$	[21, 178]
Fraction of infected CD4 T cell death <sup>+</sup>		2%	[12]
Transmission probability		$10^{-2} - 10^{-3}$	[93]
Number of founder virus per host infection <sup>a</sup>		1	[134]
Provirus copy number		1 – 8	[130, 219]

\* Increase in the exponential growth rate;

+ Attributable to CTLs recognizing a single epitope;

<sup>a</sup> In 80% of infections

**Table 2.** Fundamental parameters of HIV infection (continued)

Parameter	Unit	Estimate [range]	Ref.
Half life of HIV-infected cells <i>in vitro</i> <sup>b</sup>		4–8 days	[46,145]
Virus production / day		$10^{10}$	[190]
Half life of latent reservoir <sup>c</sup>		6–44 months	[75,233]
Virus load in plasma of untreated individuals		$10^2 - 10^7$ RNA copies / mL	[194]
Virus load under HAART		50 RNA copies / mL	[57]
Free virus half life <i>in vivo</i> (SIV)		$\sim 3-4$ min	[273]
Virus production per infected cell		$5 \times 10^4$	[43]
Point mutation rate		$2.2 \times 10^{-5} - 5.4 \times 10^{-5}$ / site / cycle	[81,122,160,161]
Recombination rate		$1.4 \times 10^{-5} - 3 \times 10^{-4}$ / site / cycle	[127,178,230,275]
Rate of HIV genetic diversity increase <i>in vivo</i> <sup>d</sup>		1 % / year in the envelope gene	[223]

<sup>b</sup> Dependent on virus and target cell

<sup>c</sup> Estimated from people under HAART

<sup>d</sup> Dependent on the genomic region

**Table 3.** Major aspects of HIV-host interaction and availability of mathematical models

Biological process	Availability of mathematical models*
Virus-target cell interaction	+++
Innate response	+
Adaptive response (CTL)	++
Neutralizing Ab response	–
Virus evolution	+++
Immune activation	+
Systemic regulation of immune homeostasis	–
Lymphoid tissue organization	–
Virus ontogeny in the target cell	–
Spatial dynamics of infection in a host	–

\* The + and – signs refer to the relative abundance of models described in the literature.

**Table 4.** Details of existing frameworks for HIV infection modelling

Processes	State space	Time scale	Nature of modelling	Ref.
Viral evolution	Wt virus, mutants, viral genomes	Short-, long-term dynamics	Deterministic (ODEs, Integro-DEs, hPDEs); Stochastic (GA) algorithms	[26, 66, 150, 182, 255]
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)	[2, 132, 182, 189, 269]
Immune responses	CTLs, CD4 T cells, DCs, NK cells, APCs	Short-term dynamics	Deterministic (ODEs); Stochastic (DEs)	[49, 119, 182, 208, 240, 261, 264]
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	[40, 76, 106, 120, 182, 185, 209, 259]

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