Modeling the immune response to HIV infection

Jessica M. Conway[1,*] and Ruy M. Ribeiro[2]

[*]corresponding author
[1]Department of Mathematics and Center for Infectious Disease Dynamics, Pennsylvania State University, University Park PA 16802, USA
[2]Laboratorio de Biomatematica, Faculdade de Medicina da Universidade de Lisboa, Portugal and Theoretical Biology and Biophysics, Los Alamos National Laboratory, Los Alamos, NM 87545, USA

Abstract

The interplay between immune response and HIV is intensely studied via mathematical modeling, with significant insights but few direct answers. In this short review, we highlight advances and knowledge gaps across different aspects of immunity. In particular, we identify the innate immune response and its role in priming the adaptive response as ripe for modeling. The latter have been the focus of most modeling studies, but we also synthesize key outstanding questions regarding effector mechanisms of cellular immunity and development of broadly neutralizing antibodies. Thus far, most modeling studies aimed to infer general immune mechanisms; we foresee that significant progress will be made next by detailed quantitative fitting of models to data, and prediction of immune responses.

Introduction

In June 5, 1981, the first five cases of individuals with a disease spectrum that later would be associated with infection by human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) were reported in the *Morbidity and Mortality Weekly Report* [1]. This was the first warning of "an epidemic that is perhaps the defining public health issue of our times" [2]. Almost 37 years later to the day, an enormous knowledge about HIV/AIDS has accumulated. And yet, HIV infection is still incurable and there is no vaccine for it. Over this time span, more than 40 million people have died of AIDS, with still 1 million deaths/year and more than 37 million people currently infected worldwide [3].

Given its relevance, HIV has been (one of) the most researched diseases in history. Work on HIV was instrumental in furthering research in numerous areas, benefitting our knowledge of multiple infections, immune mechanisms, and pathogenesis processes. Fueled by interest in HIV, dynamical mathematical modeling has seen an enormous growth, initially applied to HIV treatment with antiretroviral drugs and then expanding to model a variety of infections and immune processes. Indeed, the field is so vast now that it is impossible to review even just the modeling associated with HIV.

Here we review studies modeling HIV infection in the context of immune responses. There are many hundreds of published papers under this broad topic, and we selected to focus on those that discuss models in the context of data or that, at the very least, are heavily informed by biological knowledge. In contrast, we make almost no mention of papers on: (1) HIV treatment, (2) purely statistical models, (3) strict theoretical analyses (*e.g.*, existence or type of solutions), and (4) epidemiology of HIV. We also narrowed the scope by emphasizing more recent publications, although some older studies were judiciously added to provide context. Thus, this is not an exhaustive review of modeling of immunity in the context of HIV. It is our belief that such an attempt would be futile given the breadth of the topic. Indeed, the difficulty of the current undertaking demonstrates the vitality of the field.

We organized this review under three broad headings: 1) Understanding the course of infection; 2) Understanding immune effector mechanisms; 3) Harnessing immunity to control HIV.

Understanding the course of infection

Initial control of virus

During the prolonged asymptomatic period of HIV infection, virus is controlled at an approximate steady state by mechanisms yet not fully understood. Primary infection is characterized by a peak in viral load about 2 weeks post-infection, followed by a decline in the virus to the quasi steady-state starting from 4 to 6 weeks post-infection [4]. While modeling reveals that the peak and following reduction can be explained simply by target cell limitation [5], fitting models to patient data during the acute phase and ensuing quasi-steady state showed that some type of immune control or dynamic feedback is needed [6,7]. This was also confirmed by analyzing primary infection in a SIV-model [8].

Turnover / dynamics of lymphocytes in HIV

Although the virus appears controlled during the asymptomatic phase, there is a relentless decline in CD4+ T cells. The mechanisms responsible for that decline are not understood, despite the accumulation of many clues and the clear importance of multiple factors. One finding was that turnover of T cells (both CD4+ and CD8+) was increased in HIV infection [9,10]. These experiments on T cell turnover could only be interpreted with quantitative mathematical models [11], but the model details can influence the estimates [12–15]. On this issue and, more broadly, on estimating turnover of T cells, see the excellent discussions in [16–18].

Pathogenesis and CD4 decline

Increased turnover of both CD4+ and CD8+ T cells cannot explain decay of only CD4+ cells and the hypothesis that these decline because HIV infects and kills CD4+, but not CD8+ T cells, comes up short, since there are too few productively infected cells to explain the decline by direct killing only [19,20]. Some models based on the interactions between virus and CD4+ T cells yield a slow depletion of these cells, until a defining event (*e.g.*, an immune threshold) occurs leading to quick progression, akin to the final AIDS stage [21–27]. An alternative hypothesis, developed with the help of mathematical modeling, is that over-stimulation of the immune system by antigens and production of inflammatory mediators is responsible for accelerated death of most CD4+ T cells, leading to their population decrease [22,28–31].

Different classes of models are based on evolution of virus, to higher and higher replication rates (and thus, pathogenic potential) [32] or away from immune control [33], or on evolution of T cells leading to the accumulation of deleterious

mutations due to higher activation and replication rates of CD4+ T cells [34]. These models echo one of the first models proposed to explain HIV long-term dynamics [35].

Some studies postulate that the progression of HIV to AIDS is associated with a change in the preferential cellular target of the virus [36,37], leading to model-predicted expansion of targets for HIV with a large impact on viral load and CD4+ T cell depletion [21,38–40].

Latency

An important aspect of HIV pathogenesis is the existence of latency, that is, of CD4+ T cells infected but not producing virus. Many modeling studies analyze the processes involved in latency, measuring the decay of the latent reservoir, and evaluating protocols to flush this reservoir. We refer the reader to recent reviews of mathematical models for HIV latency [41–44].

Understanding immune effector mechanisms

Innate immune responses

The importance of the innate immune response in HIV, especially early in infection, was a late realization, and much less is known in comparison with adaptive immunity [45–47]. In part, this is because the innate response involves many different mechanisms, which are difficult to quantify, often with pleiotropic effects, including many cellular populations (dendritic cells, macrophages, natural killer (NK) cells, etc.). Therefore, fewer quantitative and modeling studies of this topic have been published; this area remains fertile ground for model-based insights.

The innate anti-retroviral factor APOBEC3G [48] is so important that HIV evolved a specific protein (vif) to counteract its effect. A mathematical model of the incorporation of APOBEC3G molecules into virions and their effect in reducing viral replication estimated that at least 80% of progeny virus must carry that molecule to effectively suppress HIV infection [49]. Other modeling studies have investigated harnessing the effects of restriction factors as a therapeutic option, including potential drug therapies targeting HIV accessory proteins such as vif [50,51].

Innate responses also promote the adaptive responses. Showa *et al.* analyzed the contribution to viral control of neutralizing antibodies vs. antibody dependent cell-mediated cytotoxicity, which involves NK or other innate immune cells [52]. And Hogue *et al.* investigated the dual role of dendritic cells in both priming the adaptive immune response and being good mediators of CD4+ T-cell infection [23]. A population of innate cells that is slightly less neglected is NK cells [53]. Interestingly, there is genetic evidence of HIV-escape from the immune control exerted by NK cells [54]. A clever modeling analysis, including NK-epitope prediction and extrapolation to population level abundance of the required NK KIR-receptor and HLA types, concluded that simple immune selection for HIV variants carrying mutated epitopes was not a likely explanation of the observation [55]. The authors of that modeling study concluded that their work "suggests that there is a significant aspect of KIR immunobiology that we do not understand", demonstrating how modeling can be used to help interpret data and falsify hypothesis.

Humoral immune responses

HIV induces a robust antibody response, but the virus can quickly mutate away from the concomitant antibody response, becoming resistant to it [56,57]. The interplay of neutralizing antibody responses and virus escape was analyzed with a mathematical model allowing cross-reactivity, which indicated that cross-neutralization potential was low and that successive rounds of escape occur in the context of relatively stable viral loads driving the diversification of the virus envelope[58]. This was a clear indication that antibodies were (at the time) an under-appreciated effector mechanism of the immune response against HIV, even though the virus can readily escape them. However, recent years have seen accelerating discoveries of broadly neutralizing antibodies (bnAbs), which are capable of neutralizing many different HIV strains [59–61]. These discoveries have led to interest in defining the role of bnAbs and their generation from an early pool of narrow-specificity antibodies [60], spurring many modeling studies [62]. bnAbs are much mutated from the germline, *i.e.*, they have suffered multiple rounds of somatic hypermutation. It therefore generally takes a number of years until bnAbs are observed in an infected patient and understanding this delay has become an important question. One well-studied modeling hypothesis has that development of bnAbs is dependent on competition between bnAbs and more specific antibodies [63–

65]. An important corollary to this hypothesis is that bnAbs do not emerge late in infection because they need to accumulate many mutations, but conversely that mutations have accumulated because bnAbs emerge late, which is a consequence of early competitive exclusion [64].

Whatever the mechanisms of generating bnAbs, their utility in HIV treatment or prevention is of keen interest. Magnus and Regoes [66] developed a probabilistic model of the stoichiometry of trimer neutralization, that is, of the number of antibodies needed to neutralize a virion, preventing it from infecting a cell. Their model was recently applied to predict and analyze antibody neutralization *in vivo* and its impact on HIV transmission [67]. One of the particularities of this latter study was the analysis and modeling of mucosal transmission. With the same objective, but taking a different approach, Wagh *et al.* [68] developed a model to define the optimal combination of bnAbs for treatment based on known *in vitro* neutralization titers of the bnAbs against 200 different viruses. This model predicts neutralization capability of combinations of bnAbs, using multiple phenotypic outcomes, such as breadth, potency of neutralization and instantaneous inhibitory potential [69]. We foresee that extending the models of stoichiometry [66,67] to the type of data sets analyzed in Wagh *et al.* [68] will afford more mechanistic insight into HIV infection and neutralization.

Cell-mediated immune responses

Most models of immune responses in HIV have analyzed the effects of cell-mediated immunity, in particular CD8+ cytotoxic T lymphocytes (CTL), and it is impossible to do justice to all the work that has been done. Importantly, modeling the cellular immune response in HIV has driven the field of mathematical modeling in immunology and led to the study of this response in many other infections (and even cancer). That is, the structure of the models and the approach taken in those other fields were borrowed from the wealth of studies in modeling cell-mediated immunity against HIV.

CD8+ T cells and CTL function

There have been two recurring themes in models of adaptive immune response research in the last decade or so. The first is a mathematical prediction of bistability between a low, "controlled" infection state, and a high, chronic steady state [29,70–74]. Indeed, recent clinical observations [75–77] point to such a possibility: suspension of drug therapy is typically followed by rebound of HIV viral loads to high, chronic-infection, but a few patients succeed in controlling infection at low viral titers. This "post-treatment control" [75–77] can be explained by a model with bistability induced by immune exhaustion, *i.e.*, immune impairment resulting from overstimulation of responses [78], providing a concrete connection of theorized infection bistability within-host [72,79–83] to empirical observations.

The second theme is related to the primary role of CD8+ T-cells in HIV infection: are responses primarily lytic or non-lytic? [84]. This debate was spurred on by contradictory experimental observations, well summarized in [84,85], including CD8+ cell depletion experiments in SIV infected macaques [86–89]. While overall the support for nonlytic responses seemed stronger, the evidence is indirect and mathematical modeling is the best platform to gain insight into the primary mechanism of CD8 effect, and to resolve these contradictions.

Analysis of the standard viral dynamics model, and comparison with viral load and CD4+ T cell data from a CD8 vaccination-challenge animal model of SHIV infection, showed that non-cytolytic control provides a better explanation for the experimental results [90]. For realistic levels of cytotoxicity, modeling predicts that immune responses dominated by non-cytolytic effector functions most positively influence disease outcome, *i.e.*, better maintenance of CD4 counts and better viral control [91]. In defense of lytic responses, Mandl *et al.* suggested that CTLs contribute significantly to infected cell killing during the acute phase of infection, but the lytic effect wanes during chronic infection, as a result of viral escape from CTL responses and/or depletion of CD4+ T cells required to stimulate CD8+ cells [79]. More detailed models of the HIV lifecycle, *e.g.*, including an eclipse phase (after infection, but before virus production), could also be compatible with a lytic effect [80,81]. In fact, a recent paper [82] analyzed such models in detail in the context of much of the experimental work on CD8+ T-cell depletion and concluded that we cannot discern from current data whether the effect of CTL is cytolytic or non-cytolytic [82]. And a recent proof-of-principle model based on observations of an untreated HIV elite controller, who experienced viral reactivation following treatment for cancer, showed viral kinetics consistent with CTL mass-action killing of both eclipse-phase and productively infected cells [83].

CTL Escape

As part of the development of immune responses, specific viral peptide sequences (epitopes) are presented to and recognized by CD8+ and CD4+ T cells, marking infected cells for attack. The process by which HIV adapts through

mutations in specific epitopes, thus escaping recognition by immune effector cells, is termed 'CTL escape.'

Some of the first estimates of the rate at which HIV accumulates CTL escape mutations were made by modeling the strength of immune selection and the fitness cost of escape variants based on direct measurements of T-cell escape and reversion in SHIV-infected pigtail macaques, assuming exponential growth of wildtype virus and escape mutant [92]. Asquith *et al.* estimated the rate of escape of 21 CTL escape variants in HIV [93]. To assess the rate of escape, they employed a coupled ODE model for dynamics of wildtype and an escape, where only the wildtype is killed by specific CTL responses, and the escape variant growth rate is hampered by a fitness cost. This type of mathematical model, which can be derived from the standard viral dynamics model [94], was widely used to investigate the properties of CTL escape [94–97]. This modeling assumed that growth and decay rates for wildtype and escape variants were constant, though they likely aren't. Ganusov *et al.* generalized the model to permit time-dependent rates, providing a theoretical basis for estimation of reduction in viral fitness and the killing rate of specific CTL responses using *in vivo* data [96].

Asquith *et al.* also quantified the efficiency of HIV-1–specific CTLs *in vivo*. They estimated that only 2% of productively infected CD4+ T-cell death is attributable to CTLs recognizing a single epitope and suggested that, therefore, lytic responses are not responsible for the majority of infected cell death [93,98]. The role of lytic vs non-lytic responses (see *CD8+ T cells and CTL function*) in CTL escape was further developed by Ganusov *et al.* [96], who compared the lytic model [93] with an alternative nonlytic model. The latter predicts a slower accumulation of the escape variant, if the total magnitude of the CD8+ response is high [96].

Single-escape models make the assumption that different escape mutations, at different epitopes, occur independently. But escapes may occur concurrently. Leviyang and Ganusov [99] extended the model [93–97] and developed a new method for analyzing longitudinal sequence data to estimate the rate of CTL escape across multiple epitopes [99]. However, in another study [100], it was shown that, for well-sampled escape data, the estimates of the model parameters including T cell killing efficacy did not depend strongly on the underlying model of escape, i.e., independently, concurrently, or in sequence [100]. Still more intricate models were developed to investigate CTL escape mutations at single or multiple sites per epitope, across multiple epitopes, or with multiple specific CTL responses, gaining realism and permitting additional insights, at the cost of significant complexity [101,102].

The potential variability of CTL escape rates throughout infection remains an important unresolved issue to be addressed by modeling. Analyses suggested that dynamics of immune escape and reversion were rapid in early infection, and much slower in later infection [93,103]; many different mechanisms have been proposed to explain this observation, such as a decreased magnitude of epitope-specific CTL responses, increased fitness cost of escape mutations, increased diversity of the CTL response, genetic interference (when multiple CD8+ T cell responses coincide and are similarly strong), increased frequency of multiple-infected cells, or the existence of an eclipse phase between cell infection and viral production [96,97,102–105]. Thus, slow escape rates do not necessarily imply inefficient CTL-mediated killing of HIV-infected cells, but may be partly a result of the specifics of the viral life cycle.

Finally, calculating escape rates at different stages of infection is, itself, problematic. Integrating genealogical inference and epidemiological modelling into previous ODE models [93–97] shows that estimates of escape rates by different methods can differ greatly [106]. Infrequent data sampling may also be a difficulty [96,102,107]. A clinical study of 125 participants with data collected frequently in the first few years of infection suggested that the majority of early CTL-related mutations did not arise *de novo* but rather had been transmitted in the infecting viral strain. Further, the incidence of new escape was low; around one third of patients did not drive an escape within the first two years and the majority only had 1 escape [108].

Harnessing immunity to control HIV

Vaccines

The search for an HIV vaccine is ongoing with attempts to induce protective antibody responses, T-cell responses, or a combination of the two. Modeling continues to provide guidance in vaccine development efforts, quantifying the level of bnAb responses [109], CTL responses [73,110,111], or CTL polyfunctionality [91] required to control infection. Modeling shows that induction of broad immune responses is a promising avenue; vaccines eliciting narrow responses, e.g., towards a single epitope, are predicted to be prone to escape [102,112]. But induction of broadly directed HIV-specific CTL immunity should reduce viral load [102] and may effectively quash early viral replication while limiting the generation of immune escape variants [112]. Further, vaccination with multiple viruses with diverse variable epitopes may increase the probability of early generation of bnAbs [62].

Immunotherapy

Therapeutic vaccines aim to modulate the immune system of HIV-infected individuals to elicit sustained virologic control without antiretroviral therapy. They have recently shown promise in randomized controlled trials and nonhuman primate studies [113,114]. Another immune-modulating strategy is based on manipulating checkpoint proteins [115,116]. Monoclonal antibodies that target these proteins have been shown to enhance HIV-specific T-cell responses in *ex vivo* studies. Clinical trials are underway to evaluate the effects of immune checkpoint inhibitors in HIV-infected individuals with cancer, in an effort to reinvigorate HIV-specific immune responses [117]. Mechanistic modeling in conjunction with data from these trials will be needed to understand the effects and optimal use of these strategies. Finally, cytokines play key role in regulating functional activities of immune effector cells; cytokines including IL-2, IL-7, IL-15 and IL-21 have shown some promise against HIV infection [118]. While there is mathematical modeling of IL-2 and IL-7 administration aimed at optimizing their use in boosting CD4+ responses [119–121], this also remains an under-studied area.

Conclusions

HIV/AIDS is one of the worst infectious diseases to ever affect humans. In 2005, the United Nations Development Program stated that "HIV/AIDS has inflicted the single greatest reversal in human development" [122] and the suffering imposed on hundreds of millions of people over the last four decades cannot be overstated. Yet, this infection has led to an unprecedented increase in our knowledge of infections and their concomitant immune responses. Modeling HIV infection and immunity has accompanied that enormous scientific development, both in terms of insights generated and approaches taken. Attempting to review the vast literature on modeling of HIV immune responses is impossible.

The most important finding of this review is that there are several areas that could benefit from investigation by modeling experts. In the near future, we envisage more work on modeling innate immune responses, the interplay of innate and acquired immunity, and the role that immunity may have in controlling the virus or eradicating latency. Although initially there was a lack of data on these topics, the last few years have seen an acceleration on the accumulation of data [47,123,124], and models should provide a framework to analyze and obtain insights from the new data sets. Further, there have been few studies where immune response data and modeling go hand in hand, for example fitting quantitative results to data. Modeling studies of HIV immune responses thus far are largely used to discuss general immune mechanisms; detailed quantitative fitting or prediction of immune responses is much more elusive. Why this is the case is not totally clear, but at least three issues are important. First, the dynamics of the immune response is much more heterogeneous than the dynamics of virus (for example, under drug treatment). Second, we still lack knowledge about important basic immune mechanisms (*e.g.*, do CD8+ T cells control virus by lytic or non-lytic mechanisms? [82]), which make it difficult to include them in the models or they must be included in very general terms. Third, there is often an unclear relation between what we would like to model and what is possible to measure, the clearest case being infected cells, which are a feature of most models, but remain difficult to measure.

Investigation into HIV/AIDS has helped usher a new era of collaboration between clinicians, virologists and immunologists on one side and mathematicians, physicists and modelers on the other. These collaborations are becoming the norm, rather than the exception, and they have provided inestimable insight into the biology and pathogenesis of this terrible disease.

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