Background: The human immune system is complex and feedback intensive. The interactions between HIV and the host immune system (Figure 1a) add more complexity, making it difficult to find a functional cure for HIV. We aim to accelerate the discovery of an HIV cure by applying System Dynamics (Figure 1b), a proven computer simulation methodology that integrates the interactions among the components of the immune system to simulate short and long term outcomes of the complex feedback systems associated with HIV and the human immune response.

Methods: We developed a systemic mathematical model of HIV infection from the infection site to the immune response, including antigen-presenting cells, lymphocytes and secondary lymphoid organs. The model development process (Figure 2) consists of three stages: 1) Conceptual design: firstly, identify dynamic interactions among the immune system components, as well as interactions between HIV and the immune system based on an extensive literature review and collaboration with leading HIV researchers; secondly, integrate these interactions into a causal loop diagram (e.g. Figure 1a) to provide a systemic view; 2) Detailed design and coding: firstly, expand the conceptual design to add more details; secondly, translate the design to mathematical equations; 3) Computer simulation and model calibration: compare the simulated outcome(s) to published data.

Results: The mathematical model reproduced key disease characteristics of HIV infection: viral load and the CD4+ T cell decline as HIV progresses from acute to established infection in untreated subjects. Plasma viral load remains undetectable for 1 to 2 weeks following HIV infection, rises rapidly to approximately 7 log10 RNA copies/mL and then declines by 2 log10 at week 3 following infection (Figure 3). Ten weeks later, a long-term set point of around 4 log10 RNA copies/mL is established. CD4+ T cell counts decline by 50% from a pre-infection value of just under 1000 cells/µL during the time-frame that viral load peaks. CD4+ T cell counts recover to just over 750 cells/µL before commencing a long-term decline of 50 - 75 cells/µL per year (Figure 3).

Conclusions: The immune system model simulator provides the opportunity for in silico hypothesis testing to better understand immune system physiology, incorporate new insights from ongoing clinical studies, and explore novel combination therapies in a broader and more time-efficient manner compared to the traditional preclinical pathway.

Figure 1a: A systemic view of the complex interactions between HIV and the host immune system. The innate and adaptive immune responses controlling HIV infection are depicted in blue. HIV’s strategies to evade and escape virtually every aspect of immune attack and to increase target cell population are depicted in red.

Figure 1b: Examples of applying system dynamics to biological systems: representing the dynamic interactions among the components and predicting systemic outcomes from the feedback structure(s).

Figure 2: The process of building a systemic computer simulation model of HIV and the immune system.

Figure 3: Simulated VIRAL LOAD and CD4+ T COUNTS versus published data of untreated acute HIV infection.

Figure 4: In Silico Preclinical Studies