Modelling the prevalence of HIV immune escape mutations in human populations

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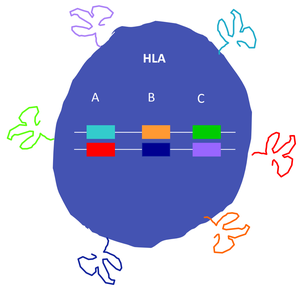
Executive Summary

HIV's capacity for rapid adaptation poses a major barrier to HIV immune control and vaccine design. Human Leukocyte Antigen (HLA) class I-restricted CD8+ T-cells drive HIV evolution through the selection of immune escape mutations in the viral genome. Escape mutations occur in a highly predictable manner based on the HLA alleles expressed by the host. Upon transmission of HIV to a host who lacks the original restricting HLA allele, many immune escape mutations will revert back to the consensus residue, presumably due to fitness costs. However, some escape mutations will persist in the population, leading to concerns that circulating HIV strains will gradually become more resistant to host immunity over time.

HIV Background

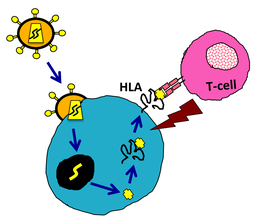
HLA Alleles

- HLA alleles help your body to identify virus-infected cells by presenting virus-derived protein fragments, or peptides, to the immune system.
- HLAs are encoded based on the enzymes they can efficiently present.
- People have 6, generally different, HLA alleles that are capable of presenting different viral peptides.
- Thousands of different HLAs are known, and distribution varies by population.

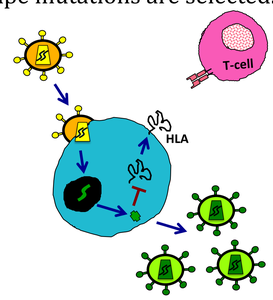


Escape Mutations

- Normally, HLA presentation of a viral peptide allows the immune system to target and destroy the infected cell.
- When HIV infects a human cell, it adapts through escape mutations.
- Escape mutation helps the virus to survive in the host by preventing presentation of its peptides by HLA. This allows the virus to continue replicating in an infected cell without recognition.
- Since the host's HLA determine what viral peptides are presented, the host HLA alleles determine what escape mutations are selected.



T-cells kill HIV-infected cells via recognition of HIV fragments bound to HLA

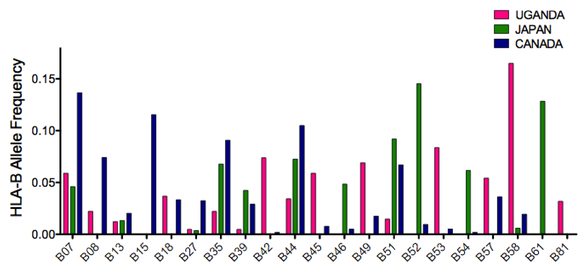


Escape mutant HIV evades T-cell killing

- If an escaped variant HIV is transmitted to a host with mismatched HLA, then it may revert to consensus type through mutation.
- However some escape mutations will persist upon transmission, leading to concerns that these may spread in the population.

HLA Alleles in the Population

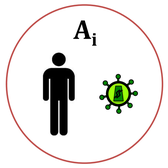
- HLA alleles occur at different frequencies in different populations.



- HLA alleles are associated with viral load set points (which influence infectivity) and rate of disease progression (risk of mortality).
- Different sets of alleles predict different rates of escape and reversion to consensus. This is represented as a rate of reversion and escape for each set of alleles.

A Basic Infection Model with HLA Alleles

The basic infection model uses an agent based approach to model HIV infection. Agent based models have the advantage of being able to incorporate heterogeneity in the agent's attributes.



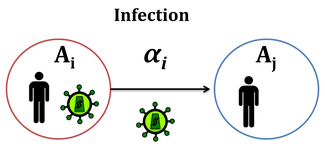
Agents have the following traits:

- A set of HLA alleles $\{A_i\}$
- HIV positive or negative
- Escaped or Consensus type HIV

State Transitions

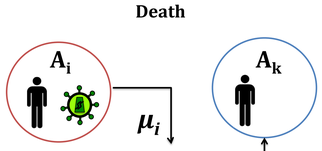
- Infection occurs between serodiscordant individuals who engage in risk behavior.
- Infection occurs with a probability per act, α_i, and transfers the HIV strain to the uninfected individual.
- Agents die with a probability per day, μ_i, and are replaced by healthy agents with new alleles.

Infection



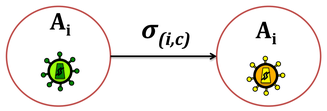
α_i is the probability per act of transmitting HIV

Death



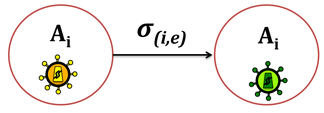
μ_i is the probability per day of dying from HIV

Reversion to Consensus



$\sigma_{(i,c)}$ is the probability per day of a mismatched virus reverting to consensus.

Consensus to Escape



$\sigma_{(i,c)}$ is the probability per day of a consensus virus escaping allele set A_i.

Project Outline

This project is an outcome of the Modelling of Complex Social Systems (MoCSSy) program hosted at the IRMACS Centre at SFU. This program supports interdisciplinary modelling through a system of mentoring, skills training, and knowledge exchange. Since inception of the program in 2008, MoCSSy projects have resulted in more than 100 peer-reviewed publications, including 7 books. Our goal is the application of innovative mathematical and computational modelling techniques to social phenomena of concern.

The HIV HLA Modelling Project is part of that initiative, combining the knowledge and analytical power of multiple disciplines to explore a problem with real-world implications. Weekly meetings began in late January 2014.

Team Members

Andrew Adams is a recent MSc graduate from SFU's mathematics department. His research focuses on understanding how high levels of variability in the HIV genome could be linked to clinical markers of disease progression in HIV infection.

Kritika Sharma is a 4th year BSc student in Kinesiology and Psychology. She is passionate about human physiology, nutrition, and behavioural neuroscience. She is interested in learning about HIV evolution, and how the virus undergoes physiological adaptations in humans. She plans on studying nursing in the near future.

Kristine Hong is a 4th year BA student in Health Sciences. Her academic interest surrounds social determinants of health, public health, and health promotion strategies for vulnerable populations. She is interested in learning about the HIV pandemic. She aims to become a health promoter after graduation.

Dr. Zabrina Brumme is an Assistant Professor in SFU's Faculty of Health Sciences. Her research integrates molecular biology, epidemiology and computational approaches to study HIV evolution in response to selection pressures imposed by its human host.

Piper Jackson is the Postdoctoral Fellow in Complex Systems Modelling at the IRMACS Centre and the Gerontology Research Centre at SFU. In addition to directing MoCSSy, Piper is part of the Ambient Assistive Living Technologies for Older Adults with Mild Cognitive Impairment (AAL-WELL) project.

Research Strategy

Through our initial research into the elements that compose this phenomenon, we have come up with two main initial research questions:

- What are the conditions necessary to generate a stable population of an escape mutant?
- How does the distribution of HLA alleles in a population affect HIV infectivity and mortality, due to the association with viral load?

We already have access to data describing the distribution of HLA alleles in given populations, and we will use this in our simulations.

Reference

Fryer, H. R., Frater, J., Duda, A., Roberts, M. G., Phillips, R. E., McLean, A. R., & SPARTAC Trial Investigators (2010). Modelling the evolution and spread of HIV immune escape mutants. PLoS pathogens, 6(11), e1001196.