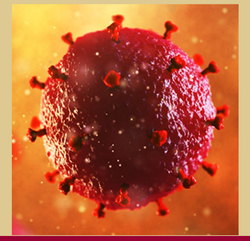
Adaptation of the HIV Viral Dynamics Model

Madeleine J. Jacobs & Dr. Yun Kang
CISA, Polytechnic Applied Mathematics



CISA Student Showcase

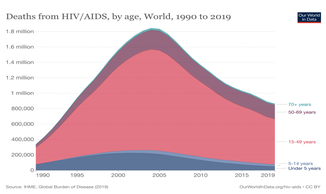
Introduction and Objectives

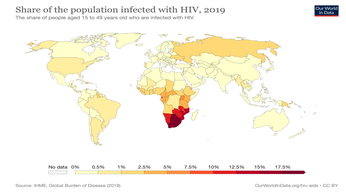
About the Virus:
- Human immunodeficiency virus (HIV) is the precursor to acquired immunodeficiency syndrome (AIDS).
- HIV is transmissible via bodily fluids through sexual intercourse, injection with a contaminated needle, breastfeeding, or perinatally in utero.
- HIV is a retrovirus, meaning that it replicates by inserting viral DNA into the genome of its host cells.
- HIV primarily targets CD4+ T-cells, immune cells that coordinate the body's response to pathogens and are crucial to proper immune function.
- Once HIV progresses to AIDS, an infected person begins to experience frequent, life-threatening opportunistic infections due to a weakened immune system.

Antiretroviral Therapy (ART):
- In 1987, the first form of antiretroviral therapy (ART) was approved for the treatment of HIV/AIDS in the U.S.
- ART therapy has markedly improved the life expectancy of someone with HIV and can even prevent the progression of the virus to AIDS if taken early enough after infection.

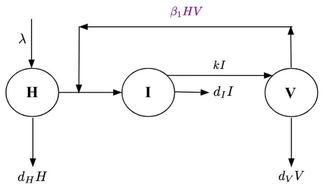
What Is Still Needed?
- As of 2021, there were 38.4 million people living with HIV. The virus is far from eradication.
- At present, ART therapy must be taken for the duration of a person's life to prevent a relapse of HIV infection due to the presence of latent (metabolically inactive) infected cells.
- A more in-depth understanding of the viral dynamics of HIV is needed to further progress research and treatment options for people affected by HIV.[3]

Research Question: How do cell-to-cell infections, latent cell populations, and ART therapy effects impact HIV viral dynamics?





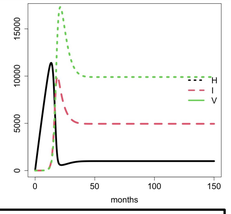
H-I-V Model of Viral Dynamics



$$H' = \lambda - \underbrace{\beta_1 HV}_{\text{virus-cell}} - d_H H$$

$$I' = \underbrace{\beta_1 HV}_{\text{virus-cell}} - d_I I$$

$$V' = kI - d_V V$$



Assumptions and Parameter Values:
- Infected cells are not able to enter a latent state
- Infections are only caused by direct virus-cell transmission
- ART therapy or other forms of immunotherapy treatment are not being taken
- $\lambda = {}^{1000}/_{\mu L - day}$, $\beta_1 = 10^{-7}$, $d_H = {}^{0.01}/_{day}$, $d_I = {}^{0.2}/_{day}$, $d_V = {}^{0.5}/_{day}$, $k = {}^{1}/_{cell-day}$
- Above parameter values used for all simulations, with $d_L = {}^{0.01}/_{day}$ and $\alpha_2 = {}^{1}/_{day}$ in adapted model simulations

Equilibrium Values and Stability:

$R_0 = \frac{\lambda \beta_1 k}{d_H d_I d_V} = \left(\frac{\lambda}{d_H}\right)\left(\frac{\beta_1}{d_I}\right)\left(\frac{k}{d_V}\right)$

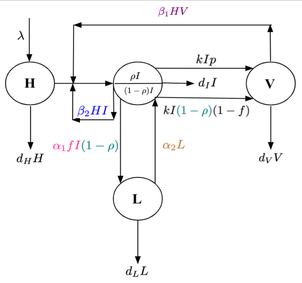
The HIV model has global stability at $z_0 = (H^*, I^*, V^*) = \left(\frac{\lambda}{d_H}, 0, 0\right)$ when $R_0 < 1$

The HIV model has global stability $z^* = (H^*, I^*, V^*) = \left(\frac{d_I d_V}{\beta_1 k}, \frac{\lambda}{d_I} - \frac{d_H d_V}{\beta_1 k}, \frac{\beta_1 \lambda k - d_H d_I d_V}{\beta_1 d_I d_V}\right)$ when $R_0 > 1$

Literature Cited

1. Hill, A.L., Rosenbloom, D.I.S., Nowak, M.A., et. al. (2018). Insight into treatment of HIV infection from viral dynamics models. *Immunological Reviews, 285,* 9-25. https://doi.org/10.1111/imr.12698
2. HIV.gov. (2022). *A Timeline of HIV and AIDS*. https://www.hiv.gov/hiv-basics/overview/history/hiv-and-aids-timeline#year-2022
3. HIV.gov. (2022, August *3). Global Statistics.* https://www.hiv.gov/hiv-basics/overview/data-and-trends/global-statistics
4. HIV.gov. (2022, June 15). *What Are HIV and AIDS?*. https://www.hiv.gov/hiv-basics/overview/about-hiv-and-aids/what-are-hiv-and-aids
5. Iwami, S., Takeuchi, J.S., Nakaoka, S., et. al. (2015). Cell-to-cell infection by HIV contributes over half of virus infection. *eLife, 4*, 1-16. https://doi.org/10.7554/eLife.08150
6. Reeves, D.B., Duke, E.R., Hughes, S.M., et. al. (2017). Ant—proliferative therapy for HIV cure: a compound interest approach. *Scientific Reports, 7*(4011). https://doi.org/10.1038/s41598-017-04160-3
7. Roser, M., & Ritchie, H. (2019, November). *HIV/AIDS*. OurWorldinData. https://ourworldindata.org/hiv-aids

Adapted Viral Dynamics Model



$$H' = \lambda - \underbrace{\beta_1 HV}_{\text{virus-cell}} - d_H H - \underbrace{\beta_2 HI}_{\text{cell-cell}}$$

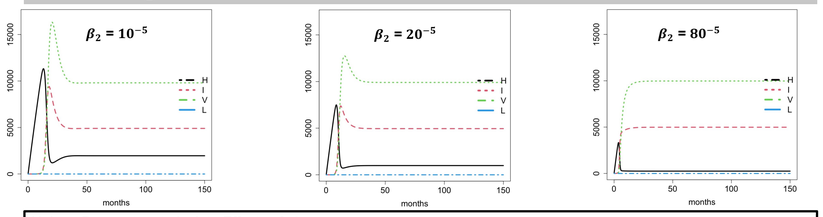
$$I' = \underbrace{\beta_1 HV}_{\text{virus-cell}} + \underbrace{\beta_2 HI}_{\text{cell-cell}} - d_I I - \underbrace{\alpha_1 fI}_{\text{P(latency)}} \underbrace{(1-\rho)}_{\text{non-resistant}} + \underbrace{\alpha_2 L}_{\text{reactivation}}$$

$$V' = kI(\rho + (\underbrace{(1-\rho)}_{\text{non-resistant}})(1-f)) - d_V V$$

$$L' = \underbrace{\alpha_1 fI}_{\text{P(latency)}} \underbrace{(1-\rho)}_{\text{non-resistant}} - d_L L - \underbrace{\alpha_2 L}_{\text{reactivation}}$$

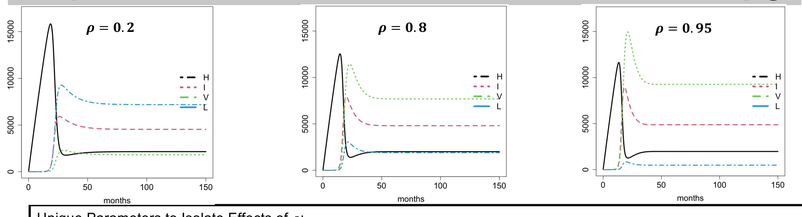
Includes four new components to address research question:
- Infectivity parameter for cell-to-cell infections, β_2
- Equation for a latent cell population, L, and parameters governing the transition of infected cells to and from a latent state of infection, α_1 and α_2
- Parameter for resistance of HIV strain to ART therapy, ρ
- Parameter for efficacy of a given form of ART therapy, f

Impact of Cell-to-Cell Infections



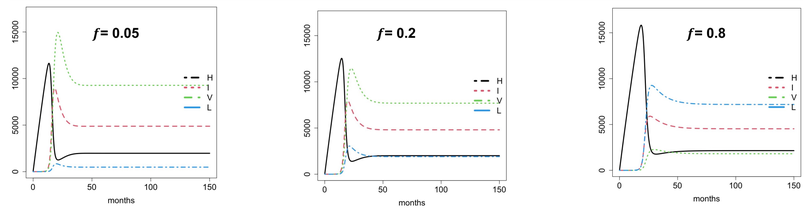
Unique Parameters to Isolate Effects of β_2:
$\rho = 1, f = 0$ (no consideration of proportion cells that are resistant to ART or of ART efficacy) , $\alpha_1 = {}^{2}/_{day}$ and varying value of cell-to-cell infectivity parameter, β_2
Observations:
Increasing the infectivity parameter for cell-to-cell infections decreases the initial spikes in both infected cell population and viral load between approximately 0 and 40 months and has no long-term effect on infected cell population and viral load. Increasing the infectivity parameter for cell-to-cell infections decreases the overall population of healthy cells, whilst leaving trends in healthy cell population over time unaffected.

Impact of Resistance to ART Therapy



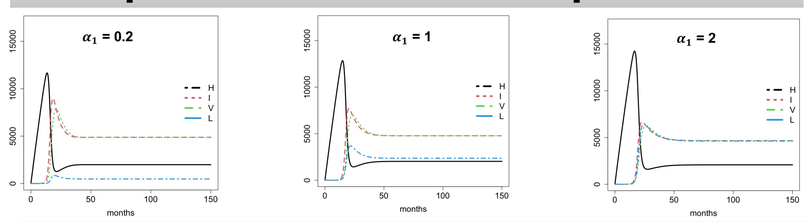
Unique Parameters to Isolate Effects of ρ:
$f = 1$ (no consideration of ART efficacy), $\alpha_1 = {}^{2}/_{day}$, $\beta_2 = 10^{-5}$, varying value of proportion of cells that are resistant to ART, ρ
Observations:
Increasing viral strain resistance to ART therapy significantly decreases the population of latent cells while maintaining trends in latent cell population over time, decreases the population of healthy cells while maintaining trends in healthy cell population over time, and increases both infected cell population and viral load while maintaining trends in infected cell population and viral load over time.

Impact of ART Efficacy



Unique Parameters to Isolate Effects of f:
$\rho = 0$ (no consideration of proportion of ART resistance), $\alpha_1 = {}^{2}/_{day}$, $\beta_2 = 10^{-5}$, varying values of ART efficacy, f
Observations:
Increasing the efficacy of ART therapy significantly increases latent cell population while maintaining trends in latent cell population over time, decreases infected cell population while maintaining trends in infected cell population over time, and increases healthy cell population while maintaining trends in healthy cell population over time.

Impact of Latent Cell Population



Unique Parameters to Isolate Effects of α_1:
$\rho = 0.5, f = 1$ (so as not to consider ART efficacy), $\beta_2 = 10^{-5}$, varying values of proportion of infected cells that enter a latent state, α_1
Observations:
Increasing the transition of infected cells to latent cells increases the population of healthy cells while maintaining trends in healthy cell population over time, slightly decreases the population of infected cells while maintaining trends in infected cell population over time, and has no impact on viral load.

Conclusions

- Cell-to-cell infectivity decreases initial spikes in but has no long-term impact on infected cell population and viral load, but the population of healthy cells decreases as cell-to-cell infections increase. **This suggests that targeting cell-to-cell infections is less important than targeting overall means of viral replication.**
- Higher efficacy of a given form of ART therapy decreases viral load as well as the population of infected cells, while increasing the population of healthy cells and of latent infected cells**. This suggests that a high-efficacy form of ART therapy is good for recovery and survival but leads to a notable population of latent infected cells that have the potential to be reactivated.**
- Greater resistance of a viral strain to ART therapy decreases both healthy cell population and latent cell population and increases both the infected cell population and viral load**. This suggests that a low-resistance form of ART therapy is good for recovery and survival but leads to a notable population of latent infected cells that have the potential to be reactivated.**
- Greater populations of latent cells increase the population of healthy cells, slightly decrease the population of infected cells, and have no impact on viral load. **This suggests that attempts to transition infected cells to latent cells could increase healthy cell population, but would not impact overall viral load.**

Acknowledgements

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