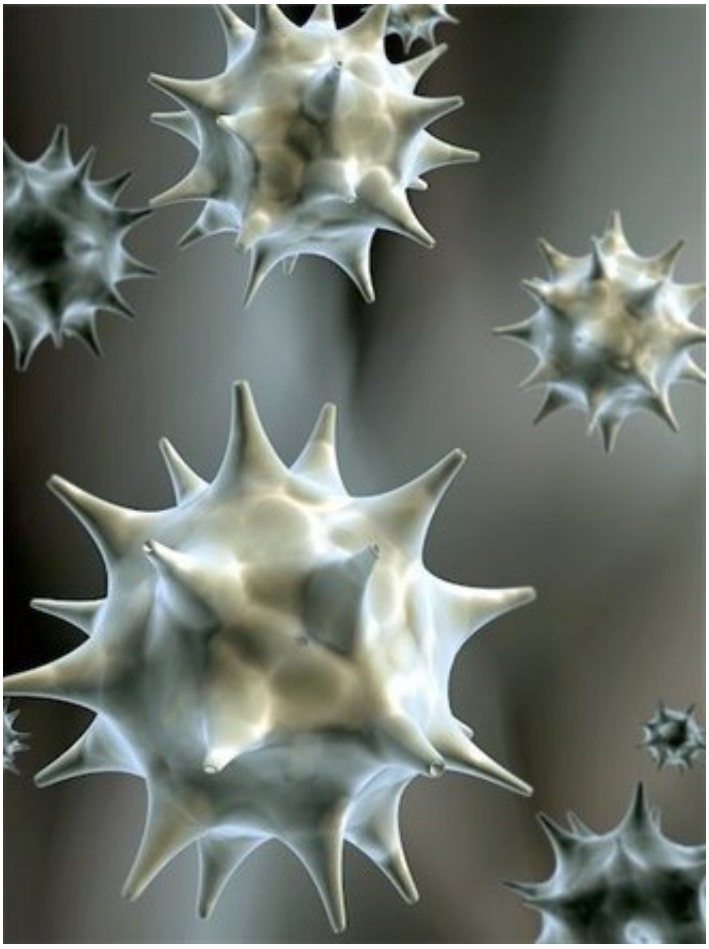
Mathematically modeling HIV drug pharmacodynamics

October 19 2017



3-D rendering of a colony of pathogen viruses. Credit: frenta / Masterfile

37 million people around the world today live with Human Immunodeficiency Virus (HIV), which is responsible for roughly 1.1

million deaths caused by AIDS-related conditions.

The virus replicates by inserting itself into the genetic code of CD4+ memory T-cells, human immune cells essential to the body's immune response. While antiretroviral therapy (ART) can interfere with this replication process, complete elimination of the virus is a challenge, since HIV maintains latent viral reservoirs within the body that can help re-establish infection. Viral reservoirs exist within resting CD4+ memory T-cells that maintain replication-competent HIV for extended time periods, allowing viral persistence even in the face of immune surveillance or antiretroviral therapy.

As Naveen Vaidya, a mathematics professor at San Diego State University, explains, "Currently there is no cure for HIV, presumably due to the establishment of latently infected cells that cannot be destroyed by available antiretroviral therapy. Hence, the primary focus of current HIV research has been to destruct HIV latent infections, and as part of this effort, initiation of antiretroviral therapy early in infection to avoid the formation of latently infected cells has been considered as potential means of successful HIV cure."

While early treatment of infection has been shown to limit and even possibly eradicate the virus in the case of pre-exposure and post-exposure prophylactic treatments, some studies have shown mixed results with regard to their effect on viral rebound. Additionally, factors determining the success of early treatment are poorly understood and the accurate timing for establishment of latent reservoirs in humans post-infection is not known. This necessitates the development of effective strategies to control latently infected cells. The pharmacodynamic properties of drugs and their effects on success of treatment have so far received little attention.

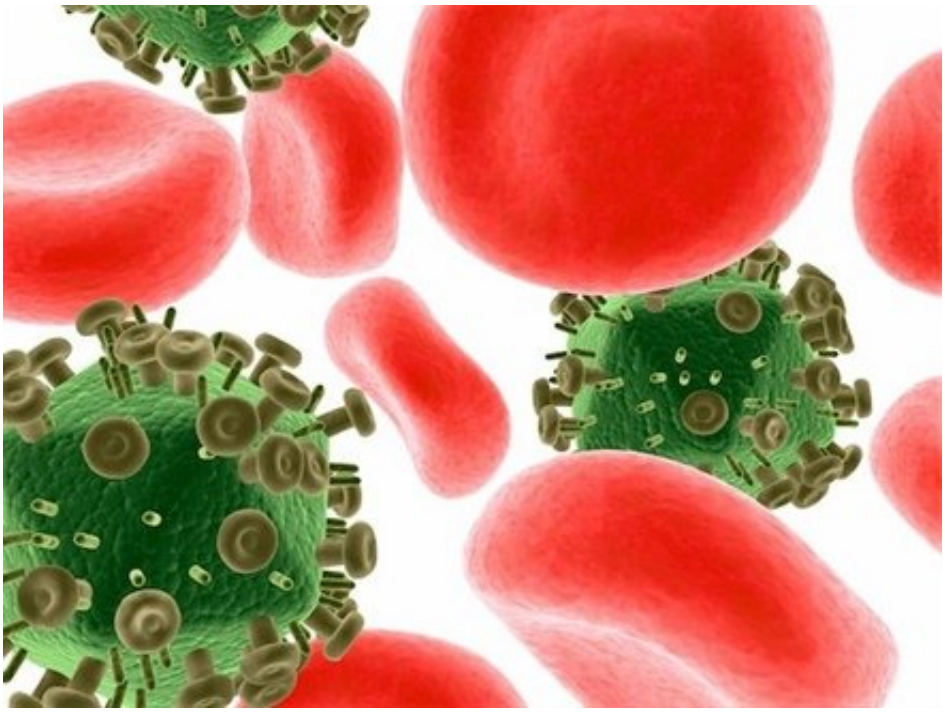
In a paper publishing this week in the *SIAM Journal on Applied*

Mathematics, Vaidya and Libin Rong, a mathematics professor at the University of Florida, propose a mathematical model that investigates the effects of drug parameters and dosing schedules on HIV latent reservoirs and viral load dynamics.

"Our research uses mathematical modeling to gain deeper insights into the effects of antiretroviral therapy on HIV latent infections, and highlights that the pharmacodynamics of drugs—and thus, the choice of drugs—used in treatment regimens can be a determinant factor for successful therapy," Vaidya says.

While previous mathematical models have helped analyze dynamics of latently-infected cells, studies exploring antiretroviral therapy and the resulting pharmacodynamics in latent reservoir dynamics are lacking.

"We have developed theories of infection threshold that help identify values of drug-related parameters for avoiding latent infections," Vaidya says. "Our results on detailed analysis of pharmacodynamics can contribute significantly to the study of drug-related parameters for controlling HIV latent infection and possibly HIV cure."



3-D-rendered illustration of blood cells and viruses. Credit: Eraxion/ Masterfile

Their model specifically focuses on the impact of antiretroviral therapy early in treatment to control latently infected cells. Using a realistic periodic drug intake scenario to obtain a periodic model system, the authors study local as well as global properties of infection dynamics, described via differential equations. The model takes into account uninfected target cells, productively infected cells, latently infected cells, and free virus concentrations as mutually exclusive compartments.

Currently available antiretroviral therapy demonstrates antiviral activity either by reducing the infection rate or viral production rate. Based on a classical dose-response relationship, the authors formulate residual viral infectivity and residual viral production during antiretroviral therapy.

Variations in specific drug parameters are shown to generate either an infection-free steady state or persistent infection. A viral invasion

threshold, derived based on the model, is seen to govern the global stability of the infection-free steady state and viral persistence.

"Pharmacodynamic parameters and dosing schedule can have significant impact on outcomes of infection dynamics in HIV patients. This effect is particularly pronounced in early and preventive therapy," Vaidya points out. The authors show that the invasion threshold is highly dependent on a few pharmacodynamic parameters. Vaidya continues, "These parameters can determine whether latent infection will establish or not; in general, treatment regimens containing drugs with a larger slope of the dose-response curve, a higher ratio of the maximum dosage to the 50% inhibitory concentration, a longer half-life and a smaller dosing interval, have the potential to prevent or postpone the establishment of viral infection. Thus, choice of drugs is key to successful cure via early therapy."

Vaidya's results demonstrate that prophylaxis or very early treatment using drugs with a good pharmacodynamics profile can potentially prevent or postpone establishment of viral infection. Only drugs with proper pharmacodynamic properties given at proper intervals can successfully combat infection. "However, once the latent infection is established, the pharmacodynamic parameters have less effect on the latent reservoir and virus dynamics," Vaidya says. "This is because the latent reservoir can be maintained by hemostasis of latently infected cells or other mechanisms rather than ongoing residual viral replications."

Efforts to maximize the impact of HIV therapy and the performance of different treatment regimens is essential to curtail the disease's burden on public health. Mathematical modeling offers a theoretical framework to evaluate drug pharmacodynamics and their antiviral effects on HIV dynamics.

"Mathematical models can be used to analyze and simulate a large

number of treatment scenarios, which are often impossible and/or extremely difficult to study in vivo and/or vitro experimental settings," as Vaidya explains. "The results from these models can also provide novel themes for further experiments. For example, our modeling results in this study suggest that the drugs with a larger slope of the drug-response curve, such as protease inhibitors, are more effective in controlling latent infections, and thus such drugs in treatment regimens need to be included in further experimental studies."

While these theoretical results offer useful ideas to develop treatment protocols, these in vivo and in vitro experimental studies are needed to properly design treatment regimens for successful control of latent infections. "Our group and collaborators will continue to develop mathematical models to study effects of pharmacodynamics on latent infection of HIV, including the models with the emergence of drug resistance," says Vaidya. "Furthermore, our future modeling study will include the effects of drug pharmacodynamics on treatment outcomes in HIV patients under conditioning of drugs of abuse, and identifying optimal control regimens for successful reduction of latent infections."

Provided by Society for Industrial and Applied Mathematics

Citation: Mathematically modeling HIV drug pharmacodynamics (2017, October 19) retrieved 25 April 2024 from https://phys.org/news/2017-10-mathematically-hiv-drug-pharmacodynamics.html

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