Mathematical models to better combat HIV

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The first few hours to days following exposure to human immunodeficiency virus (HIV) can be of critical importance in determining if infection occurs in a patient. But the low numbers of viruses and infected cells at this stage makes it very difficult to study these events in humans or animal models.

Theoretical mathematical models can help analyze viral dynamics in this early phase, and hence offer insights into therapeutic and prevention strategies, as evidenced by a paper published last month in the *SIAM Journal on Applied Mathematics*.

In a paper titled "Stochastic Analysis of Pre- and Postexposure Prophylaxis against HIV Infection," authors Jessica Conway, Bernhard Konrad, and Daniel Coombs present theoretical models of HIV dynamics immediately following exposure to the virus, thus providing a method to study infection and treatment at these early stages, as well as come up with preemptive strategies for prevention.

Different classes of HIV drugs target different phases of the viral life cycle. For instance, drugs may prevent the viral genetic material from being integrated into the host cell or disrupt the formation of new viral particles. "In models of chronic infection, the different drug mechanisms end up having similar effects in mathematical models," explains author Daniel Coombs. "But during early infection, every step of the life cycle is critical for the small virus population to persist in the host, and this leads to interesting differences between the efficacies of different drugs in this phase."

The authors create stochastic models to analyze viral dynamics and to understand how protective or preventative drug treatment prior to or immediately following exposure can act to reduce risk of infection under various scenarios.

"There's a lot of discussion in public health circles about the potential of pre- and post-exposure prophylaxis (PrEP and PEP respectively) against HIV," says Coombs. "Clinical practices for PEP are based on empirical findings with older, less effective drugs, while PrEP is very new and still under development." For this reason, clinical trials of PrEP and PEP often show variable success, making it hard to predict their effectiveness.

"We used stochastic models to investigate different choices of treatment strategies for both PEP and PrEP. Our results are in good agreement with clinical findings, and also show possible directions for future investigation," says Coombs.

The paper proposes a simple and a more complex model. The simple one-compartment model of HIV infection uses a mathematical formula that incorporates the dynamics between replication-competent and -incompetent viruses, as well as infected cells in the eclipse phase (when they do not produce virus) and in the productive phase (when they do). The formula also includes the rate of infection of new cells, the rate of viral clearance (due to removal or inactivation), as well as the interaction of different types of drugs. The complex (two-compartment) model is similar, but additionally incorporates different cell types and transport dynamics—two factors that are also important in the initiation of HIV infection.

While comparing drugs for PrEP, the authors conclude that reverse transcriptase inhibitors, which inhibit the process of transcription of the virus's RNA into DNA in the host cell, are somewhat more effective

than protease inhibitors, which inhibit viral RNA replication. Protease inhibitors act by inactivating the protease enzyme, a molecule that speeds up breakdown of proteins in organisms."The differences are small, though, and other practicalities (like toxic side-effects, or drug costs) might well be more important in making the best choice," says Coombs. For PEP, most models and trials predictably show that fast initiation of therapy is important. The authors' models indicate that risk reduction falls to below 15% after a three-day delay of treatment, and a two-week treatment regimen is shown to work essentially as well as the current recommendation of four weeks.

The models presented in the paper deal with HIV infection following blood exposure, hence focusing mainly on occupational exposure. Mechanisms leading to infection by sexual exposure are more complicated, but the general framework of the model may be applied to cases of sexual infection. With more experimental data on anatomy, physiology and nature of virus-host interactions, the current model can be reconstructed to capture the stages of sexual exposure. The concern regarding development of drug-resistant HIV following PEP and PrEP can also be addressed with more extensive modeling with the help of additional experimental data from animal models.

"It's tough to study the early events in HIV infection experimentally, so it's very natural to use mathematical modeling to investigate the possible effects of drug treatment. On the other hand, because experimental work is so difficult, it's not obvious how to construct a model," says Coombs, explaining the complexities of mathematically modeling HIV. "For this reason, we used the simplest model we could think of that still captures the essentials of early viral replication. There's a lot of scope to develop more complex models of early infection, and especially to use information gleaned from experimental infections of animals. On the other hand, because our models are so simple, they could be adapted to other viral infections such as HCV or influenza in the future."

More information: Stochastic Analysis of Pre- and Postexposure Prophylaxis against HIV Infection, *SIAM Journal on Applied Mathematics*, 73(2), 904 (Online publish date: April 18, 2013). The source article is available for free access until August 31, 2013: epubs.siam.org/doi/abs/10.1137/120876800

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