How a Math Equation Revolutionized Treatment for HIV

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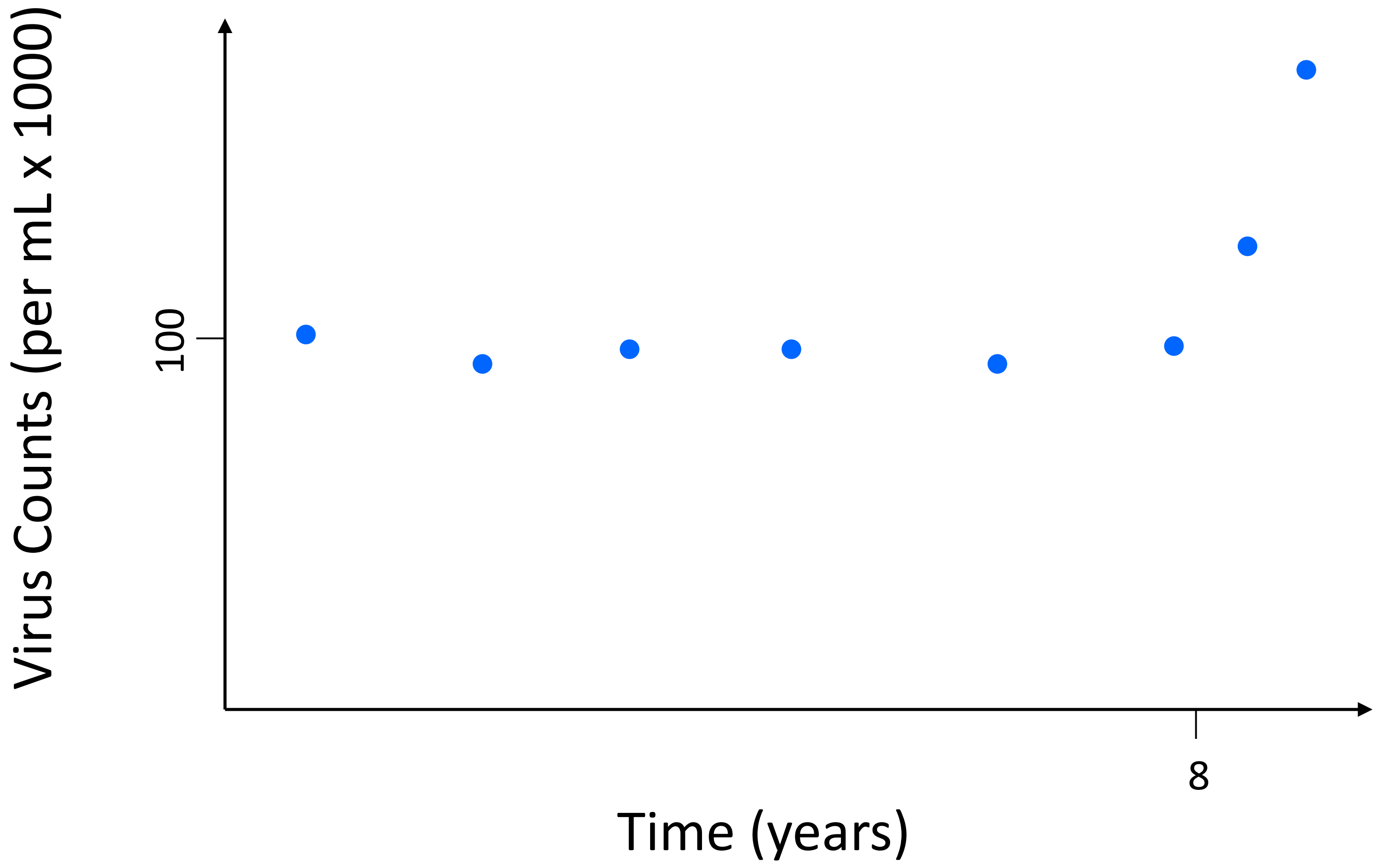
Human Immunodeficiency Virus (HIV)

- Virus was identified in 1983, and determined to cause severe immunosuppression
- Led to acquired immunodeficiency syndrome (AIDS) and opportunistic fatal infections
- Very fast mutation rate
- Zidovudine (AZT) approved in 1987

Typical HIV Levels Without Treatment



How to Best Give HIV Therapy?

- Let's say we have Drugs A & B to use
- If we give Drug A until it stops working, then we can follow it with Drug B
- If we give Drugs A & B at same time, will that be better or worse?
- Depends on whether resistance is present at beginning

Why Is Resistance Important?

- If the virus is already resistant to both A & B, then giving both at the same time does not help
- It is similar to giving a single drug
- Are there lots of chances for mutation during therapy?
- Would need to have reproduction, and some thought that mostly occurred years after initial infection

HIV Lifespan: One Piece of the Puzzle

- It was thought that HIV had an average lifespan of at least several years, possibly ten years or more
- In a 1995 paper, David Ho and Alan Perelson used math to more accurately estimate the virus lifespan
- This might help settle the debate about why the available drugs stopped working after six months or so

The Mathematics Behind the Result

- Let V = concentration of virions in a patient's blood plasma at time t
- We'll look at its rate of change with respect to time, $\frac{dV}{dt}$
- This is called a derivative
- $\frac{dV}{dt}$ = Rate in – Rate out

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- Let Rate in = P = production rate function
- Rate out = cV where c is an unknown constant
- Our model is: $\frac{dV}{dt} = P - cV$
- This is called a differential equation
- c is the "per capita" death rate (per day)
- $1/c$ is the average lifespan (number of days)
- Solving the differential equation and fitting the curve to data would allow us to estimate c
- We can't solve it because we don't know P

Drugs Eliminate the Unknown Function P

- Drugs that are protease inhibitors prevent HIV from producing new copies of itself.
- Data collected while treating with a protease inhibitor can be modeled using the same equation as before, but with the unknown production rate function P replaced by zero.

$$\frac{dV}{dt} = P - cV \qquad \Rightarrow \qquad \frac{dV}{dt} = -cV$$

- This is an equation we can solve!

Solving the Differential Equation

$$\frac{dV}{dt} = -cV$$

$$\frac{1}{V}\,dV = -c\,dt$$

$$\int \frac{1}{V}\,dV = \int -c\,dt$$

$$\int \frac{1}{V}\,dV = -ct + C_1$$

$$\ln|V| + C_2 = -ct + C_1$$

$$\ln V = -ct + C_3$$

$$e^{\ln V} = e^{-ct + C_3}$$

$$V = e^{-ct}\,e^{C_3}$$

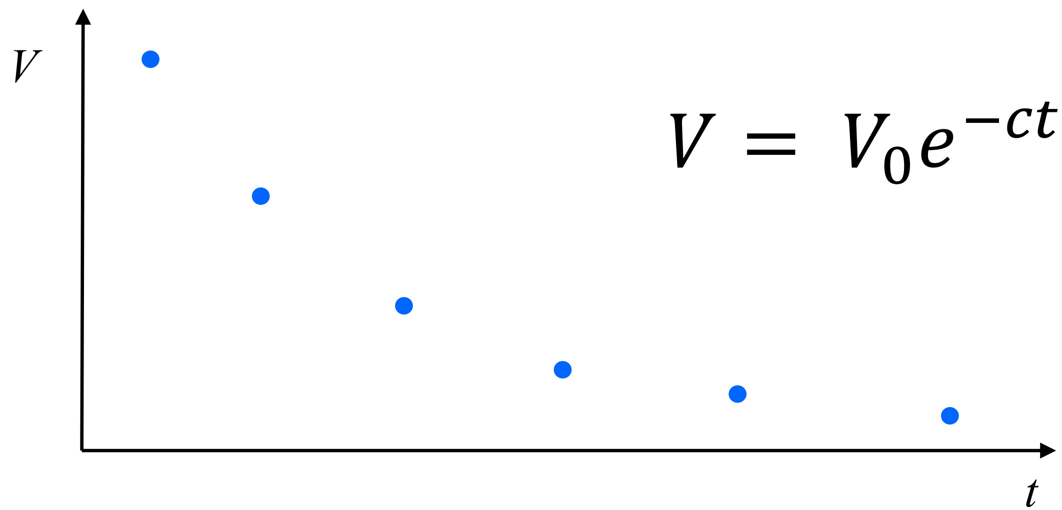
$$V = C_4 e^{-ct}$$

$$V = V_0\,e^{-ct}$$

where V_0 is the virus concentration at time $t = 0$.

Relating Data to the Mathematics

- Blood samples were collected from patients starting at the protease inhibitor treatment time.
- If the viral concentrations from these samples are plotted, the graph should show exponential decay.



$$V = V_0 e^{-ct}$$

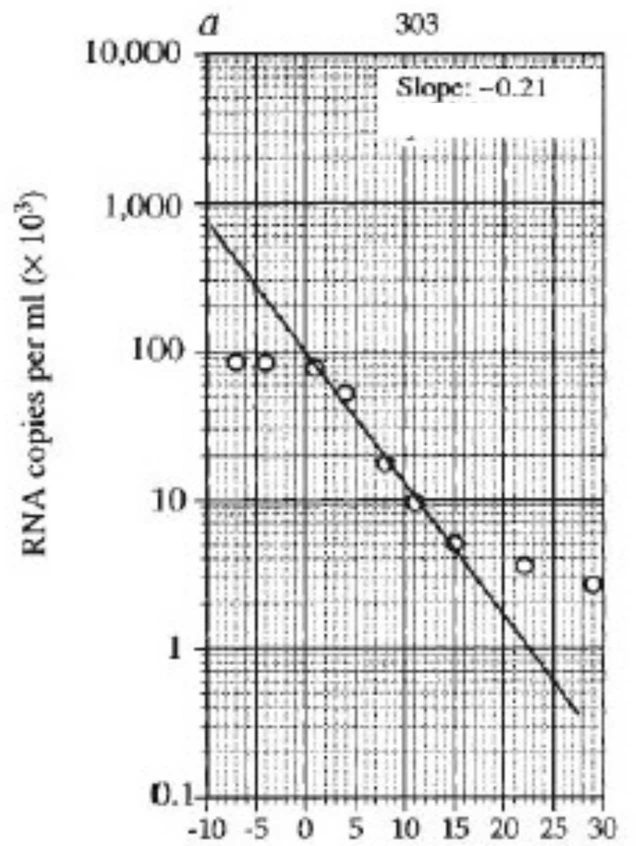
Rescaled Graph

It is easier to model the natural log of the data:

$$
\begin{aligned}
y &= \ln(V) \\
&= \ln(V_0\, e^{-ct}) \\
&= \ln(V_0) + \ln(e^{-ct}) \\
&= \ln(V_0) - ct\ln(e) \\
&= \ln(V_0) - ct \\
&= -ct + \ln(V_0)
\end{aligned}
$$

which is a line with slope $-c$.

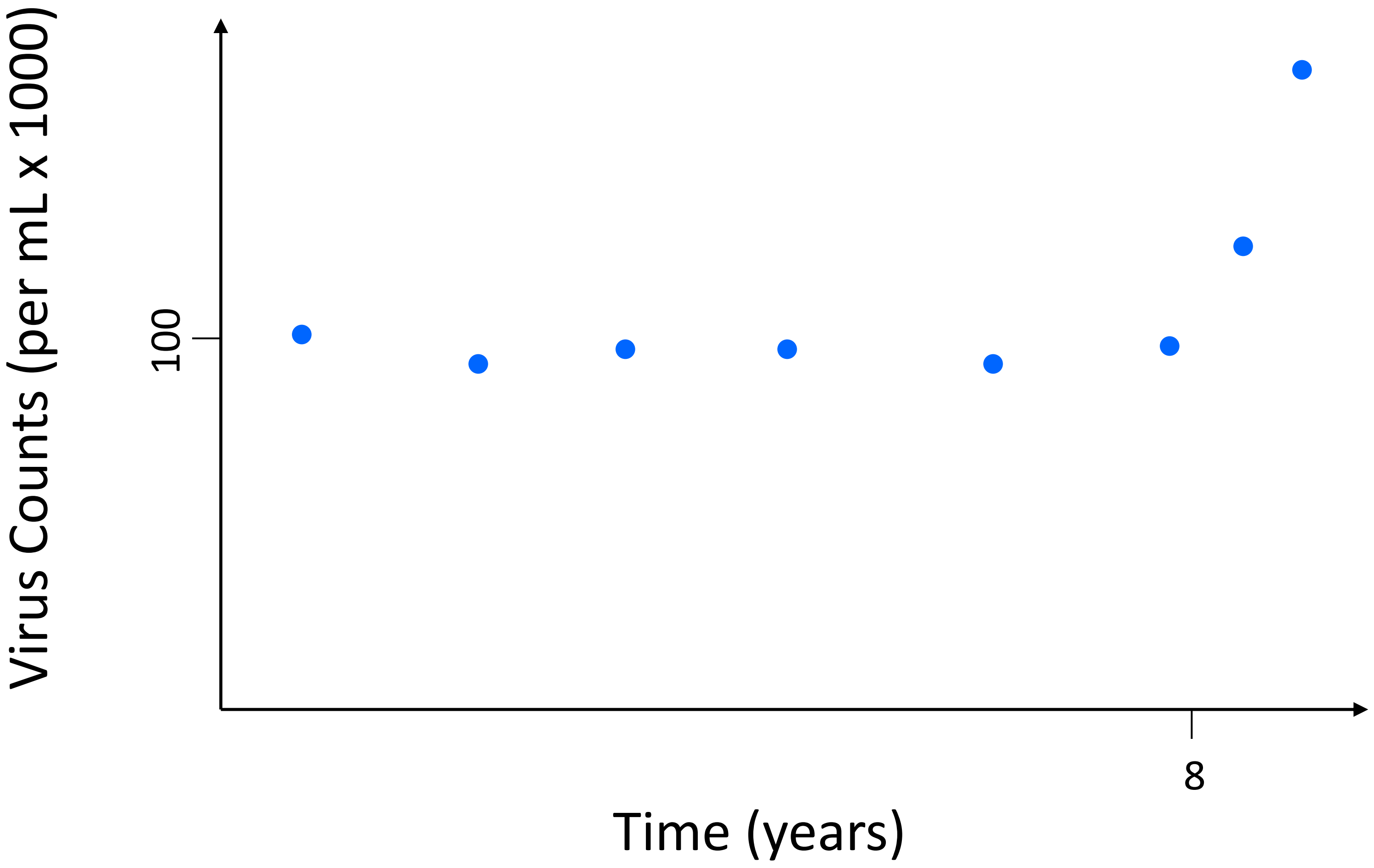
Rescaled Graph – Patient Data



c = 0.21 => lifespan = 1/0.21 ~ 4.8 (days)

Ho, Neumann, Perelson, et al. Nature, 1995.

Typical HIV Levels Without Treatment



How did HIV therapy stop working?

- If resistance is present at the beginning, treat with one drug at a time
- Were there resistant virions before therapy started?
- Or did resistant virions arise after therapy started?
- The realization that so many virions were produced in a short time indicated resistant mutations likely occur after therapy started
- This meant combination therapy could help therapies work longer

Why Would Combination Be Better?

- Suppose mutations resistant to a single drug happen at a rate of about 1 in every new 10,000 virions (probability = 1/10,000, or 1 in ten thousand)
- If we give Drug A alone, we expect resistance to arise in the time it takes 10,000 virions to be produced
- If we give Drug B after Drug A stops working, we expect similar numbers for Drug B
- If we give Drugs A and B simultaneously, the probability of a virion resistant to both is 1/100,000,000 (1 in 100 million)
- Instead of needing 20,000 new virions, we expect to need about 100 million, or 5000 times as many

Summary of Probabilities

- Resistance to Drug A: 10,000 virions
- Resistance to Drug B: 10,000 virions
- So, resistance to Drug A followed by Drug B: 20,000 virions needed
- Resistance to A & B given simultaneously: 100,000,000 virions needed

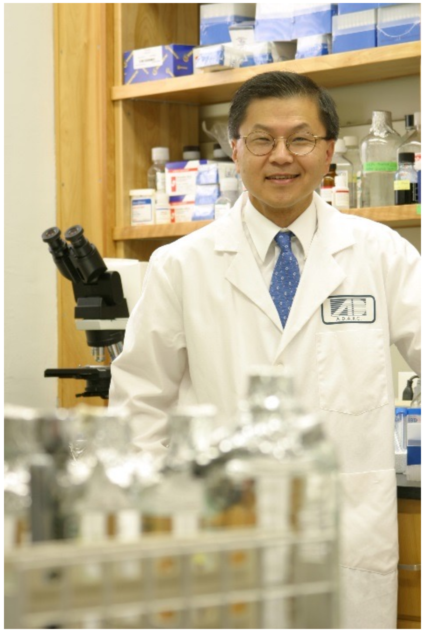
Result

- Patients were no longer given single-drug therapy.
- “Drug cocktails” became the standard of care

Photo by Helen Moore

1996 Person of the Year

- David Ho was named Time magazine's Person of the Year for this and other work that improved treatments for HIV+ patients.



References

- Ho, Neumann, Perelson, et al. (1995) Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. *Nature* Vol. 373, pp. 123-126. (Cited by over 4000 other papers.)
- *Virus Dynamics*. (2001) Nowak and May.

Recommendations for BioPharma Career

- Differential equations
- Other mathematics
- Computer programming
- Statistics
- Data mining
- Communication and teamwork skills