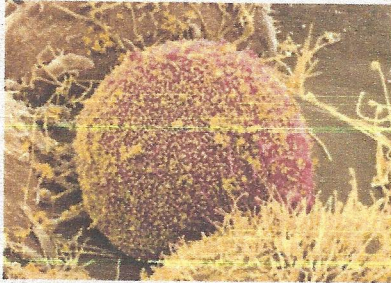


Is AIDS an Invariably Fatal Disease?

by Ivan Kramer



Cell infected with HIV

This essay will address and answer the question: Is the acquired immunodeficiency syndrome (AIDS), which is the end stage of the human immunodeficiency virus (HIV) infection, an invariably fatal disease?

Like other viruses, HIV has no metabolism and cannot reproduce itself outside of a living cell. The genetic information of the virus is contained in two identical strands of RNA. To reproduce, HIV must use the reproductive apparatus of the cell it invades and infects to produce exact copies of the viral RNA. Once it penetrates a cell, HIV transcribes its RNA into DNA using an enzyme (reverse transcriptase) contained in the virus. The double-stranded viral DNA migrates into the nucleus of the invaded cell and is inserted into the cell's genome with the aid of another viral enzyme (integrase). The viral DNA and the invaded cell's DNA are then integrated, and the cell is infected. When the infected cell is stimulated to reproduce, the proviral DNA is transcribed into viral DNA, and new viral particles are synthesized. Since anti-retroviral drugs like zidovudine inhibit the HIV enzyme reverse transcriptase and stop proviral DNA chain synthesis in the laboratory, these drugs, usually administered in combination, slow down the progression to AIDS in those that are infected with HIV (hosts).

What makes HIV infection so dangerous is the fact that it fatally weakens a host's immune system by binding to the CD4 molecule on the surface of cells vital for defense against disease, including T-helper cells and a subpopulation of natural killer cells. T-helper cells (CD4 T-cells, or T4 cells) are arguably the most important cells of the immune system since they organize the body's defense against antigens. Modeling suggests that HIV infection of natural killer cells *makes it impossible for even modern antiretroviral therapy to clear the virus* [1]. In addition to the CD4 molecule, a virion needs at least one of a handful of co-receptor molecules (e.g., CCR5 and CXCR4) on the surface of the target cell in order to be able to bind to it, penetrate its membrane, and infect it. Indeed, about 1% of Caucasians lack coreceptor molecules, and, therefore, are completely *immune* to becoming HIV infected.

Once infection is established, the disease enters the acute infection stage, lasting a matter of weeks, followed by an *incubation period*, which can last two decades or more! Although the T-helper cell density of a host changes quasi-statically during the incubation period, literally billions of infected T4 cells and HIV particles are destroyed—and replaced—daily. This is clearly a war of attrition, one in which the immune system invariably loses.

A model analysis of the essential dynamics that occur during the incubation period to invariably cause AIDS is as follows [1]. Because HIV rapidly mutates, its ability to infect T4 cells on contact (its infectivity) eventually increases and the rate T4 cells become infected increases. Thus, the immune system must increase the destruction rate of infected T4 cells as well as the production rate of new, uninfected ones to replace them. There comes a point, however, when the production rate of T4 cells reaches its maximum possible limit and any further increase in HIV's infectivity must necessarily cause a drop in the T4 density leading to AIDS. Remarkably, about 5% of hosts show no sign of immune system deterioration for the first ten years of the infection; these hosts, called *long-term nonprogressors*, were originally

therapy before 1987, it is reasonable to conclude that the survival of the 1985 Maryland AIDS patients was not significantly influenced by zidovudine therapy.

The small but nonzero value of the immortal fraction S_i obtained from the Maryland data is probably an artifact of the method that Maryland and other states use to determine the survivability of their citizens. Residents with AIDS who changed their name and then died or who died abroad would still be counted as alive by the Maryland Department of Health and Mental Hygiene. Thus, the immortal fraction value of $S_i = 0.0665$ (6.65%) obtained from the Maryland data is clearly an upper limit to its true value, which is probably zero.

Detailed data on the survivability of 1,415 zidovudine-treated HIV-infected hosts whose T4 cell densities dropped below normal values were published by Easterbrook et al. in 1993 [3]. As their T4 cell densities drop towards zero, these people develop clinical AIDS and begin to die. The longest survivors of this disease live to see their T4 densities fall below 10 cells/mm³. If the time $t = 0$ is redefined to mean the moment the T4 cell density of a host falls below 10 cells/mm³, then the survivability of such hosts was determined by Easterbrook to be 0.470, 0.316, and 0.178 at elapsed times of 1 year, 1.5 years, and 2 years, respectively.

A least-squares fit of the survival fraction function in (2) to the Easterbrook data for HIV-infected hosts with T4 cell densities in the 0–10 cells/mm³ range yields a value of the immortal fraction of $S_i = 0$ and a survival half-life of $T_{1/2} = 0.878$ year [4]; equivalently, the average survival time is $T_{\text{aver}} = 1.27$ years. These results clearly show that zidovudine is not effective in halting replication in all strains of HIV, since those who receive this drug eventually die at nearly the same rate as those who do not. In fact, the small difference of 2.5 months between the survival half-life for 1993 hosts with T4 cell densities below 10 cells/mm³ on zidovudine therapy ($T_{1/2} = 0.878$ year) and that of 1985 infected Marylanders not taking zidovudine ($T_{1/2} = 0.666$ year) may be entirely due to improved hospitalization and improvements in the treatment of the opportunistic infections associated with AIDS over the years. Thus, the initial ability of zidovudine to prolong survivability with HIV disease ultimately wears off, and the infection resumes its progression. Zidovudine therapy has been estimated to extend the survivability of an HIV-infected patient by perhaps 5 or 6 months on the average [4].

Finally, putting the above modeling results for both sets of data together, we find that the value of the immortal fraction falls somewhere within the range $0 < S_i < 0.0665$ and the average survival time falls within the range $0.960 \text{ years} < T_{\text{aver}} < 1.27 \text{ years}$. Thus, the percentage of people for whom AIDS is not a fatal disease is less than 6.65% and may be zero. These results agree with a 1989 study of hemophilia-associated AIDS cases in the USA which found that the median length of survival after AIDS diagnosis was 11.7 months [5]. A more recent and comprehensive study of hemophiliacs with clinical AIDS using the model in (2) found that the immortal fraction was $S_i = 0$, and the mean survival times for those between 16 to 69 years of age varied between 3 to 30 months, depending on the AIDS-defining condition [6]. **Although bone marrow transplants using donor stem cells homozygous for CCR5 delta32 deletion may lead to cures, to date clinical results consistently show that AIDS is an invariably fatal disease.**

Related Problems

1. Suppose the fraction of a cohort of AIDS patients that survives a time t after AIDS diagnosis is given by $S(t) = \exp(-kt)$. Show that the average survival time T_{aver} after AIDS diagnosis for a member of this cohort is given by $T_{\text{aver}} = 1/k$.
2. The fraction of a cohort of AIDS patients that survives a time t after AIDS diagnosis is given by $S(t) = \exp(-kt)$. Suppose the mean survival for a cohort of hemophiliacs diagnosed with AIDS before 1986 was found to be $T_{\text{aver}} = 6.4$ months. What fraction of the cohort survived 5 years after AIDS diagnosis?

Murder at the Mayfair Diner

by Tom LoFaro



The Mayfair diner in Philadelphia, PA

Dawn at the Mayfair Diner. The amber glow of streetlights mixed with the violent red flash of police cruisers begins to fade with the rising of a furnace orange sun. Detective Daphne Marlow exits the diner holding a steaming cup of hot joe in one hand and a summary of the crime scene evidence in the other. Taking a seat on the bumper of her tan LTD, Detective Marlow begins to review the evidence.

At 5:30 a.m. the body of one Joe D. Wood was found in the walk in refrigerator in the diner's basement. At 6:00 a.m. the coroner arrived and determined that the core body temperature of the corpse was 85 degrees Fahrenheit. Thirty minutes later the coroner again measured the core body temperature. This time the reading was 84 degrees Fahrenheit. The thermostat inside the refrigerator reads 50 degrees Fahrenheit.

Daphne takes out a fading yellow legal pad and ketchup-stained calculator from the front seat of her cruiser and begins to compute. She knows that Newton's Law of Cooling says that the rate at which an object cools is proportional to the difference between the temperature T of the body at time t and the temperature T_m of the environment surrounding the body. She jots down the equation

$$\frac{dT}{dt} = k(T - T_m), \quad t > 0, \quad (1)$$

where k is a constant of proportionality, T and T_m are measured in degrees Fahrenheit, and t is time measured in hours. Because Daphne wants to investigate the past using positive values of time, she decides to correspond $t = 0$ with 6:00 a.m., and so, for example, $t = 4$ is 2:00 a.m. After a few scratches on her yellow pad, Daphne realizes that with this time convention the constant k in (1) will turn out to be *positive*. She jots a reminder to herself that 6:30 a.m. is now $t = -1/2$.

As the cool and quiet dawn gives way to the steamy midsummer morning, Daphne begins to sweat and wonders aloud, "But what if the corpse was moved into the fridge in a feeble attempt to hide the body? How does this change my estimate?" She re-enters the restaurant and finds the grease-streaked thermostat above the empty cash register. It reads 70 degrees Fahrenheit.

"But when was the body moved?" Daphne asks. She decides to leave this question unanswered for now, simply letting h denote the number of hours the body has been in the refrigerator prior to 6:00 a.m. For example, if $h = 6$, then the body was moved at midnight.

Daphne flips a page on her legal pad and begins calculating. As the rapidly cooling coffee begins to do its work, she realizes that the way to model the environmental temperature change caused by the move is with the unit step function $\mathcal{U}(t)$. She writes

$$T_m(t) = 50 + 20\mathcal{U}(t - h) \quad (2)$$

and below it the differential equation

$$\frac{dT}{dt} = k(T - T_m(t)). \quad (3)$$

Daphne's mustard-stained polyester blouse begins to drip sweat under the blaze of a midmorning sun. Drained from the heat and the mental exercise, she fires up her cruiser and motors to Boodle's Café for another cup of java and a heaping plate

perfectly described by Newton's Law of Cooling, this topic is covered in most forensic medicine texts. In reality, the cooling of a dead body is determined by more than just Newton's Law. In particular, chemical processes in the body continue for several hours after death. These chemical processes generate heat, and thus a near constant body temperature may be maintained during this time before the exponential decay due to Newton's Law of Cooling begins.

A linear equation, known as the *Glaister equation*, is sometimes used to give a preliminary estimate of the time t since death. The Glaister equation is

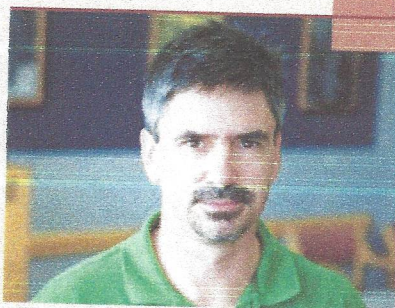
$$t = \frac{98.4 - T_0}{1.5} \quad (4)$$

where T_0 is measured body temperature (98.4° F is used here for normal living body temperature instead of 98.6° F). Although we do not have all of the tools to derive this equation exactly (the 1.5 degrees per hour was determined experimentally), we can derive a similar equation via linear approximation.

Use equation (1) with an initial condition of $T(0) = T_0$ to compute the equation of the tangent line to the solution through the point $(0, T_0)$. Do not use the values of T_m or k found in Problem 1. Simply leave these as parameters. Next, let $T = 98.4$ and solve for t to get

$$t = \frac{98.4 - T_0}{k(T_0 - T_m)} \quad (5)$$

ABOUT THE AUTHOR



Courtesy of Tom LoFaro

Tom LoFaro is a professor and chair of the Mathematics and Computer Science Department at Gustavus Adolphus College in St. Peter, Minnesota. He has been involved in developing differential modeling projects for over 10 years, including being a principal investigator of the NSF-funded IDEA project (<http://www.sci.wsu.edu/idea/>) and a contributor to CODEE's ODE Architect (Wiley and Sons). Dr. LoFaro's nonacademic interests include fly fishing and coaching little league soccer. His oldest daughter (age 12) aspires to be a forensic anthropologist much like Detective Daphne Marlow.