Pergamon

Mathl. Comput. Modelling Vol. 23, No. 3, pp. 1–14, 1996

0895-7177/96 $15.00 + 0.00

0895-7177(95)00229-4

The Impact of Zidovudine (AZT) Therapy on the Survivability of Those with the Progressive HIV Infection

I. KRAMER
Physics Department
University of Maryland—Baltimore County
Catonsville, MD 21228, U.S.A.

(Received and accepted July 1995)

Abstract—An analysis of the data regarding the impact of zidovudine therapy on the survivability of those with progressive HIV disease demonstrates that this therapy extends longevity for perhaps 5.5 months on the average but does not prevent the disease from eventually being fatal. All of the benefits of zidovudine therapy in extending survivability appear to accrue within a relatively short treatment period, perhaps within a few months, but the effectiveness of this drug wanes in time, suggesting that zidovudine therapy could eventually be stopped without influencing survivability. Since the efficacy of zidovudine therapy in extending survivability appears to be independent of the stage of the HIV infection in infecteds whose CD4 T-cell densities fall below 200 cells/mm^3, zidovudine therapy should be initiated when the patient's infection reaches a potentially fatal stage. Zidovudine therapy may be viewed as causing the HIV infection to regress to a previous stage of the disease, but the infection's progression promptly resumes and follows a course similar to one uninfluenced by zidovudine.

Keywords—Zidovudine (ZDV), Azidothymidine (AZT), HIV infection, AIDS survivability, CD4 T-cell density.

STUDIES TESTING ZIDOVUDINE EFFICACY IN PROGRESSIVE HIV DISEASE

Following reports that zidovudine (formerly azidothymidine (AZT)) was effective in slowing the progression to clinical AIDS in cohorts infected with the human immunodeficiency virus (HIV) or in staving off death in those that had already developed AIDS [1–4], three recent studies [5–7] have added new data from which the efficacy of zidovudine therapy can be ascertained and quantified.

Like all other viruses, HIV cannot reproduce on its own, requiring the reproductive apparatus of a cell that the virion "infects." HIV gains entrance to a target cell mainly through a glycoprotein (gp120) of the viral envelope protein. Since HIV is a retrovirus (re = reverse, tr = transcriptase), it contains the viral enzyme RNA-dependent DNA polymerase (reverse transcriptase) that transcribes DNA from the virion's two identical strands of RNA containing all of virion's genetic information. The double-stranded DNA made by the virion's reverse transcriptase migrates into the nucleus of a target cell and is inserted with the aid of another viral enzyme (integrase) into the cell's genome. Once the virion's DNA is integrated into the cell's reproductive apparatus, exact copies of the virus are produced when the infected cell is stimulated to replicate. The proviral DNA is transcribed into viral RNA, and messenger RNA (mRNA) and new virions are synthesized which can infect new cells. Since zidovudine inhibits the HIV reverse

transcriptase enzyme and stops proviral DNA chain synthesis *in vitro*, the drug held out promise of being effective in slowing or stopping the progression of the infection *in vivo*.

HIV infects or attacks the T-helper cells of the host's immune system by binding to the CD4 molecule on the cell's surface. T-helper cells (CD4 T-cells) are critical to the mounting of a defense against any infection. Although the immunological parameters of the immune system of a host infected with HIV change quasi-statically after the acute infection stage, literally billions of CD4 T-cells and HIV virions are destroyed—and replaced—**daily** during an incubation period that could last two decades. Since the peripheral blood of a person with a CD4 T-cell density of 10^3 cells/mm^3 has approximately 5 billion T-helper cells, this daily turnover of CD4 T-cells during the incubation period represents a large fraction of the total.

The immune system in about 95% of those infected with HIV gradually loses its long battle with HIV; the CD4 T-cell density in the peripheral blood of these infecteds inexorably drops from normal levels towards zero. When an infected's CD4 T-cell density drops to around the abnormal value of 200 cells/mm^3, AIDS can spontaneously develop, and the HIV infection has reached its potentially fatal stage. Remarkably, about 5% of those infected with HIV show no sign of immune system deterioration within the first ten years of the infection; these "long term nonprogressors" (LTNP) may be immune to developing AIDS from the HIV infection and are being intensively studied today.

For the purposes of clarity, the term "clinical" AIDS used in this paper will be defined as the Centers for Disease Control (CDC) definition before 1993, i.e., having the HIV infection and acquiring one of the opportunistic infections characteristic of AIDS. In early 1993, the CDC expanded the definition of AIDS to include those infecteds whose CD4 T-cell density fell below 200 cells/mm^3 without developing any of the characteristic infections of the disease [8], a definition that will be called "bureaucratic" AIDS in this paper.

The 1986 study that led to the widespread use of zidovudine in the treatment of HIV infecteds was conducted by Fischl *et al.* [1]. Fischl chose 282 HIV subjects either with clinical AIDS manifested by *Pneumocystis carinii* pneumonia **alone** or with advanced AIDS-related complex. The subjects in this double-blind controlled trial were stratified according to CD4 T-cell density and then randomly assigned to either a zidovudine-receiving or placebo group. Because the measured survivability of the zidovudine group was so much greater than that of the control group, the study was abruptly stopped at 24 weeks, and zidovudine was made available to all of its subjects.

The Veterans Affairs Cooperative Study (VA study) by Hamilton *et al.* [5] was a four-year, randomized, double-blind trial of zidovudine efficacy involving a cohort of 338 symptomatic HIV infected individuals, free of clinical or bureaucratic AIDS, with CD4 T-cell densities between 200 and 500 cells/mm^3. The cohort was split into a group that was immediately given zidovudine therapy (the "early" treatment group) and a second group whose members initially received a placebo but were switched to zidovudine therapy after developing clinical or bureaucratic AIDS (the "late" treatment group). It is important to note that this study was controlled for age, race, CD4 T-cell density, as well as other factors. The conclusion of this study was that early zidovudine therapy in symptomatic patients with the HIV infection **delays** the onset of clinical AIDS, but does **not** increase survivability and was associated with more side effects.

The Concorde study was a three-year, randomized, double-blind study of zidovudine efficacy involving a cohort of 1749 **symptom-free** HIV infected individuals [6]. In this study, over 40% of the subjects had CD4 T-cell densities greater than 500 cells/mm^3 while less than 8% of the subjects had densities below 200 cells/mm^3. Thus, the mean CD4 T-cell density of the Concorde cohort at baseline was significantly higher than that of the Veterans Affairs cohort.

The conduct of the Concorde trial was very similar to that of the Veterans Affairs study. The Concorde cohort was similarly split into a group that was immediately given zidovudine therapy (the "immediate" treatment group) and a second group whose members initially received a placebo but were switched to zidovudine therapy after developing ARC, clinical AIDS, or acquir-

ing a persistently low CD4 T-cell density (the "deferred" treatment group). As with the Veterans Affairs study, the Concorde study was controlled for age and CD4 T-cell density. The conclusion of the Concorde study was that despite the large difference in the quantity of zidovudine used in the treatment of these two groups, there was no statistically significant difference in the groups' three-year progression rates to AIDS or death. Although the number of subjects in this study who developed clinical AIDS or died outnumbered the sum of those in all other published trials in symptom-free and early symptomatic infection combined, early use of zidovudine in symptom-free HIV infected adults was **not** found effective in either delaying the onset of clinical AIDS or increasing survivability.

It is important to realize that the common conclusion of the Veterans Affairs and Concorde studies that the **duration** of zidovudine therapy has no significant effect on survivability with the HIV infection does **not** mean that this therapy is ineffective in extending longevity.

Interestingly, both the Veterans Affairs and the Concorde studies found that the CD4 T-cell density of the group immediately treated with zidovudine was shifted to a value lying somewhere between 30–50 cells/mm^3 higher than the group in which zidovudine therapy was deferred. This shift remained essentially constant throughout the study periods although the **rate of decline** in the CD4 T-cell density was about the same in both groups. Although it may be tempting to interpret this upward CD4 T-cell density shift due to early zidovudine therapy as a strengthening of the immune system, it must be remembered that a similar upward CD4 T-cell density shift is recorded in smokers, with the increase directly proportional to the number of packs of cigarettes smoked per day [9]. Furthermore, the average CD4 T-cell density of smokers falls faster than nonsmokers following infection with HIV [9]. Since smoking clearly does not strengthen the immune system against HIV, the higher absolute value in the CD4 T-cell density in the immediate zidovudine therapy group is not indicative of a strengthened immune system.

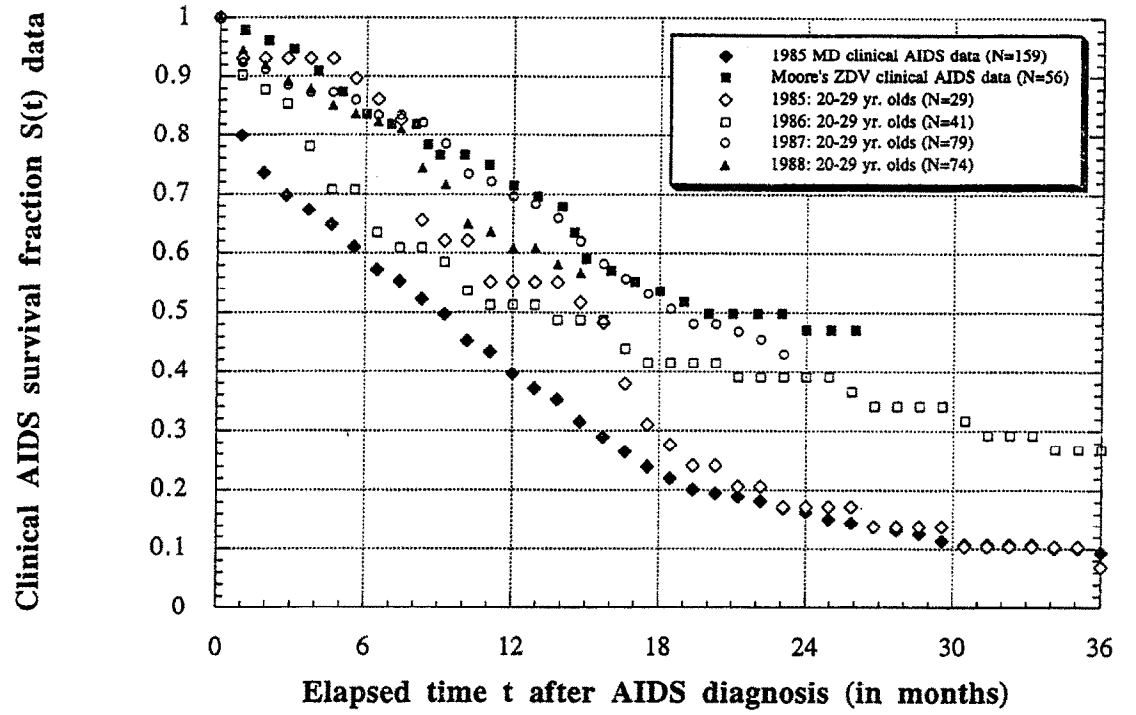
A study that enables the survivability of zidovudine treated HIV infecteds who develop bureaucratic AIDS to be calculated was conducted by Easterbrook *et al.* [7]. The Easterbrook data enables the integration of the results of the Fischl, Veterans Affairs, and Concorde studies into a comprehensive analysis of the impact of zidovudine therapy on survivability with progressive HIV disease.

Before this synthesis is undertaken, however, it is important to revisit and analyze the frequently cited study of Moore *et al.* that concluded that zidovudine therapy substantially improved survival with the HIV infection [4]. It will now be shown that, contrary to belief, *no conclusion* regarding zidovudine's impact on the survivability of those with clinical AIDS can be drawn for the data presented in this study.

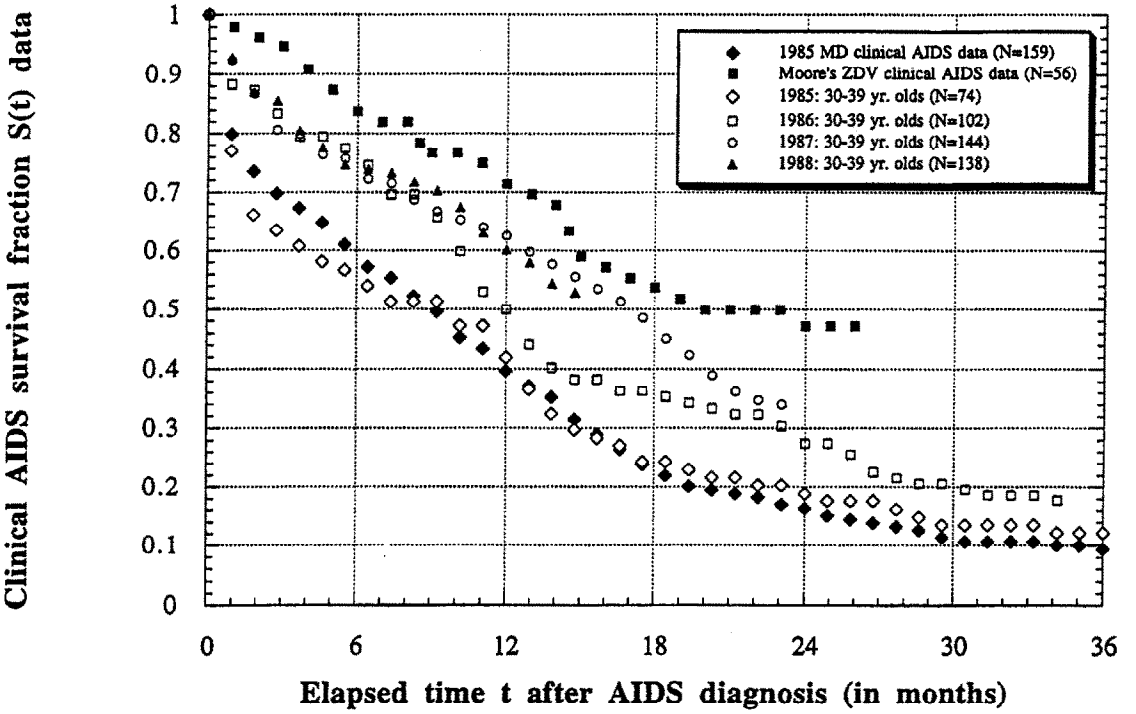
AN ANALYSIS OF MOORE'S ZIDOVUDINE EFFICACY STUDY

Since zidovudine (ZDV) was licensed for use and became widely available in April, 1987, Marylanders diagnosed with clinical AIDS between April 1987 and June 1989 were enlisted in the Moore *et al.* study [4]. Although a total of 352 out of the 714 Marylanders in the study received some zidovudine therapy, only 56 received zidovudine therapy from the moment they were diagnosed with clinical AIDS. It must be emphasized that this was not a double-blind controlled study. For example, of the 714 Marylanders with clinical AIDS, zidovudine therapy was received by 56% of those younger than 30 years old, 41% of those older than 45 years old, 59% of homosexual men, but only 38% of the intravenous drug users. Since HIV infected intravenous drug users as a whole are less likely to promptly seek out adequate medical treatment for the opportunistic infections that befall them, those receiving zidovudine therapy in the Moore study are younger and more likely to receive prompt medical treatment than those that did not, a bias that will turn out to be very important.

The survival fraction data for the 56 members of the Moore study who received zidovudine therapy immediately after AIDS diagnosis [4, Figure 1] is reproduced in Figures 1a and 1b here



(a) Comparing Moore's zidovudine (ZDV) clinical AIDS survival fraction data [4] with Maryland survivability data for 20–29 year old cohorts.



(b) Comparing Moore's zidovudine (ZDV) clinical AIDS survival fraction data [4] with Maryland survivability data for 30–39 year old cohorts.

Figure 1.

for convenience ("Moore's ZDV clinical AIDS data"). Because the Moore study was **not** a controlled one, there is no control cohort receiving placebos, and there is no conclusive way of judging the significance of the survivability data for Moore's zidovudine cohort. Thus, to be able to judge the significance of this zidovudine survival data, it is necessary to compare it to survival

fraction data for other groups of Marylanders with clinical AIDS who did not receive zidovudine therapy. The Maryland clinical AIDS survivability data was provided to this author as part of a grant he received from the AIDS Administration of the Maryland Department of Health and Mental Hygiene in 1990 [10].

The survivability data for **all** Marylanders diagnosed with clinical AIDS in 1985 is shown in Figures 1a and 1b. The 1985 Maryland AIDS survivability curve does not differ markedly from the survivability curve for those not receiving zidovudine therapy in the Moore paper [4, Figure 1]. The 1985 Maryland survivability curve is the only such curve plotted here since it does not differ significantly from the 1983 or 1984 Maryland survivability curves. It is clear from Figure 1a that the survivability of Moore's cohort receiving zidovudine therapy is significantly greater than that of the 1985 Maryland cohort that never received zidovudine therapy. Is this improvement in survivability due to zidovudine therapy?

The Maryland data clearly shows that survivability with clinical AIDS is a sensitive function of the infected cohort's race and age at AIDS diagnosis, among other factors [10]. For example, the survivability data clearly shows that the mean survival time **increases** as the age at AIDS diagnosis of the cohort **decreases**.

The separate survivability curves for cohorts of Marylanders in the 20–29 year old range diagnosed with clinical AIDS in the years 1985, 1986, 1987, and 1988 are shown in Figure 1a. This data suggests that long term survivability with clinical AIDS steadily improved in the years from 1985 to 1987. The improvement in survivability from 1985 to 1986 could only be due to increased success in the treatment of characteristic infections of AIDS and could not have been caused by zidovudine therapy since zidovudine was not in general use before April 1987. Could the improvement in AIDS survivability from 1986 to 1987 be due to zidovudine therapy?

Although Moore *et al.* do not give the age distribution of the 56 members of the zidovudine-receiving cohort, the survivability data plotted in Figure 1a clearly suggest that most if not all of the members of the Moore zidovudine-receiving cohort are in the 20–29 year old age group. However, Moore's subjects were drawn from those diagnosed with clinical AIDS after April 1987 but before June 1989. Thus, all things being equal, it is probable that less than half of Moore's 56 subjects were diagnosed with AIDS in 1987, and these subjects are distributed over **all** age brackets. The survival curve for the 1987 Maryland 20–29 year old group shown in Figure 1a has 79 subjects in it, with, therefore, probably much less than half of these being on zidovudine therapy. Since the survival curve for the 1987 Maryland 20–29 year old group is virtually identical to that of Moore's zidovudine clinical AIDS group, those 20–29 year olds receiving zidovudine therapy had **about the same survivability** as those that did not. This result suggests that zidovudine may have had little or no effect in improving the survivability with clinical AIDS.

To test the above conclusion, the survivability curves for Marylanders aged 30–39 diagnosed with clinical AIDS in the years 1985, 1986, 1987, and 1988 are shown in Figure 1b. For comparison, the survivability curves of Moore's zidovudine clinical AIDS group and all Marylanders diagnosed with clinical AIDS in 1985 are also shown in Figure 1b. Comparing the survivability of the 20–29 and 30–39 year old groups in each respective year shows that the mean survivability of the 20–29 year old group of any given year is generally greater than that of the 30–39 year old group of the same year. Furthermore, the survivability for the 30–39 age group steadily improved from 1985 to 1987, as seen in Figure 1b, to a point where this curve lies not far below the Moore zidovudine curve. Since the 1987 30–39 age group has 144 subjects in it, zidovudine therapy could not have greatly influenced this group's survivability curve since the Moore zidovudine group is estimated to have less that 30 people overlapping this group. Since the survivability of the 1987 20–29 year old group is expected to be higher at any given time than the 1987 30–39 year old group, it can be inferred that the survivability curve of the 1987 20–29 year old group should be very close to the Moore zidovudine clinical AIDS group, a conclusion that turns out to be the case as seen in Figure 1a. Thus, the ability of zidovudine to influence survivability with clinical AIDS is unproven by the Moore data.

Finally, it is worth pointing out that the survivability for the 20–29 year old group actually **fell** on the average from 1987 to 1988 while that for the 30–39 year old group remained about the same. Considering that it was probable that zidovudine therapy was **more** prevalent in 1988 than in 1987, the lack of demonstrable improvement in survivability with the HIV infection from 1987 to 1988 in Maryland again suggests that the efficacy of zidovudine is unproven by the Moore study.

ZIDOVUDINE THERAPY AND BUREAUCRATIC AIDS SURVIVABILITY

Detailed data on the survivability of 1,415 zidovudine-treated HIV infecteds who developed bureaucratic AIDS was compiled by Easterbrook *et al.* [7]. The CD4 T-cell density of each subject in the study at initiation of zidovudine therapy was defined as the last CD4 density in the 2 months before starting zidovudine therapy. At initiation of zidovudine therapy, 476 patients had clinical AIDS (median CD4 T-cell density = 77 cells/mm^3), 687 had symptomatic HIV disease (median CD4 T-cell density = 194 cells/mm^3), 194 were asymptomatic (median CD4 T-cell density = 269 cells/mm^3), and in 58 patients, the clinical status was unknown. Thus, at initiation most of the subjects of this study had CD4 T-cell densities below 200 cells/mm^3, the threshold of bureaucratic AIDS.

When the subjects' CD4 T-cell density first fell below 200 cells/mm^3, they were placed in subgroups, each characterized by a different range of CD4 T-cell densities. The survivability of each subgroup as a function of the elapsed time in that subgroup was then calculated from recorded data. The main results of this study are reproduced in Table 1 here for convenience (see [7, Table 1]).

Table 1. Fraction of AZT-treated HIV infecteds surviving from first CD4 count within defined ranges (Easterbrook data [7]).

CD4 T-cell density range (cells/mm^3)	Number of patients	Fraction Surviving		
		12 months	18 months	24 months
151–200	186	0.974	0.946	0.765
101–150	180	0.932	0.817	0.673
51–100	152	0.870	0.682	0.514
0–50	552	0.685	0.428	0.257
41–50	142	0.832	0.584	0.364
31–40	134	0.766	0.467	0.295
21–30	126	0.635	0.357	0.227
11–20	88	0.598	0.339	0.159
0–10	62	0.470	0.316	0.178

These results suggest that the survivability curves for all of the CD4 T-cell subgroups can be generated from the survivability curve for the 151–200 CD4 T-cell density subgroup using the following simplified model. It will now be assumed that the CD4 T-cell densities of all of the members of a subgroup fall in such a way so that **all** of its surviving members will **simultaneously** become members of the subsequent subgroup with a lowered CD4 density range. Note that this assumption allows the rates of decline in the CD4 T-cell density of every member of a CD4 T-cell subgroup to be **different** in general. If this assumption is true, then the survivability curve for each subgroup can be generated from the subgroup with the highest CD4 T-cell density

range, the 151–200 CD4 T-cell density subgroup. The good agreement with the data that will be obtained with this model suggests that it is a good approximation to reality.

Assuming this model to be true, if the survivability as a function of time t of the 151–200 CD4 T-cell density subgroup is denoted by $S(t)$, then the survival curve $S_i(t)$ for the **remaining** subgroups are given by $S_i(t) = S(t + t_i)/S(t_i)$, where t starts from 0 in this formula and where the index i describes the CD4 T-cell range of the subgroup. The parameters t_i will be regarded as "lag" times and are determined by a least-squares fit to the survival curve data. Although this model cannot be expected to be precisely correct, it does however give very good agreement with the data as shall now be shown. Since $S(t)$ essentially represents the survivability curve for HIV infecteds whose CD4 T-cell densities drop below 200 cells/mm^3, $S(t)$ is the survivability curve for infecteds who develop bureaucratic AIDS.

Focusing on the first four subgroups in Table 1, a simultaneous fit to all the survivability data was sought using 3 independent "lag" times t_i as parameters and the following very simple 2-parameter function to represent the bureaucratic AIDS survivability curve $S(t)$:

$$S\,(t;\, n, t_p) = \exp\left(-\frac{t}{t_p}\right) \sum_{k=0}^{n} \frac{(t/t_p)^k}{k!}, \tag{1}$$

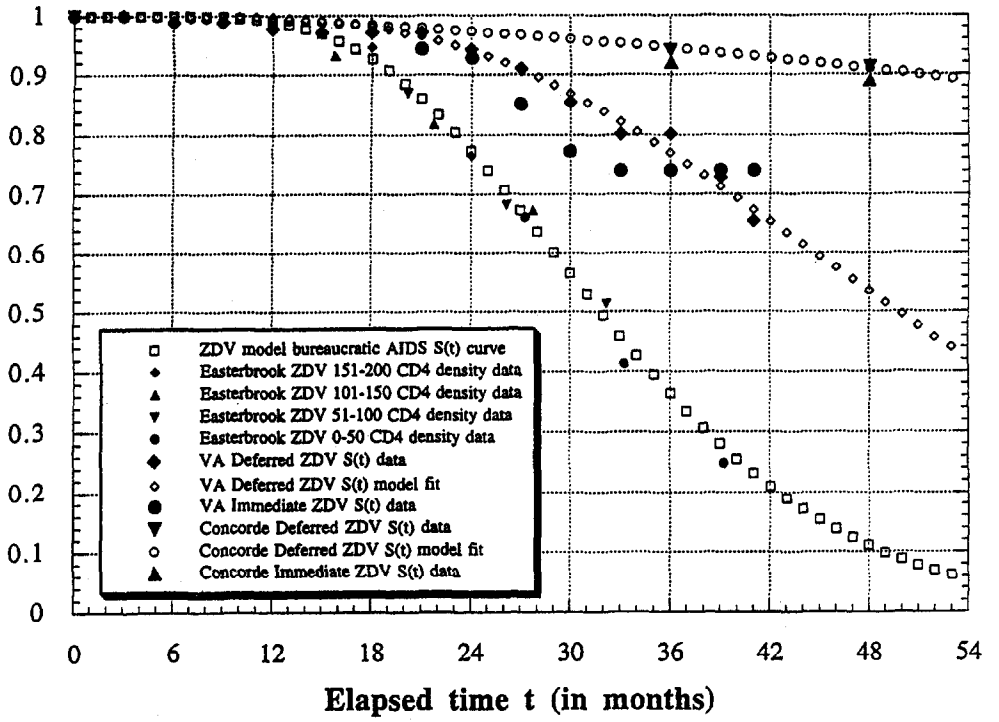
where the integer n and the time t_p are also fit parameters. The data and the best fit to it are shown in Figure 2a; the fit is obviously very good and has a norm of residuals of 8.0%. The bureaucratic AIDS survivability curve $S(t;\, n, t_p)$ is best represented by choosing $n = 7$ and $t_p = 4.15$ months in equation (1). The "lag" times for each of the indicated CD4 T-cell subgroups generated by the fit turned out to be $t_{101\text{–}150} = 3.76$ months, $t_{51\text{–}100} = 8.18$ months, and $t_{0\text{–}50} = 15.3$ months. A major result of this model is that it enables the calculation of the survivability curve 15.3 months **beyond** Easterbrook's experimental range of 24 months, as seen in Figure 2a.

One of the results of the model fit is an estimate of the time dependence of the mean CD4 T-cell density below 200 cell/mm^3 of HIV infecteds receiving zidovudine therapy. For example, at time $t = 0$, the mean CD4 T-cell density of members of the 151–200 cell/mm^3 subgroup is 175 cells/mm^3, while at time $t_{101\text{–}150} = 3.76$ months, the mean CD4 T-cell density of this subgroup has fallen to 125 cells/mm^3. Thus, points on the time-dependent mean CD4 T-cell density curve can be calculated using the values for the 3 "lag" times generated by the fit to the survivability data for the three different CD4 T-cell subgroups, and the results are plotted in Figure 2b. To test these model results, we will compare them with actual case data in the literature for the time dependence of the CD4 T-cell density in HIV infecteds.

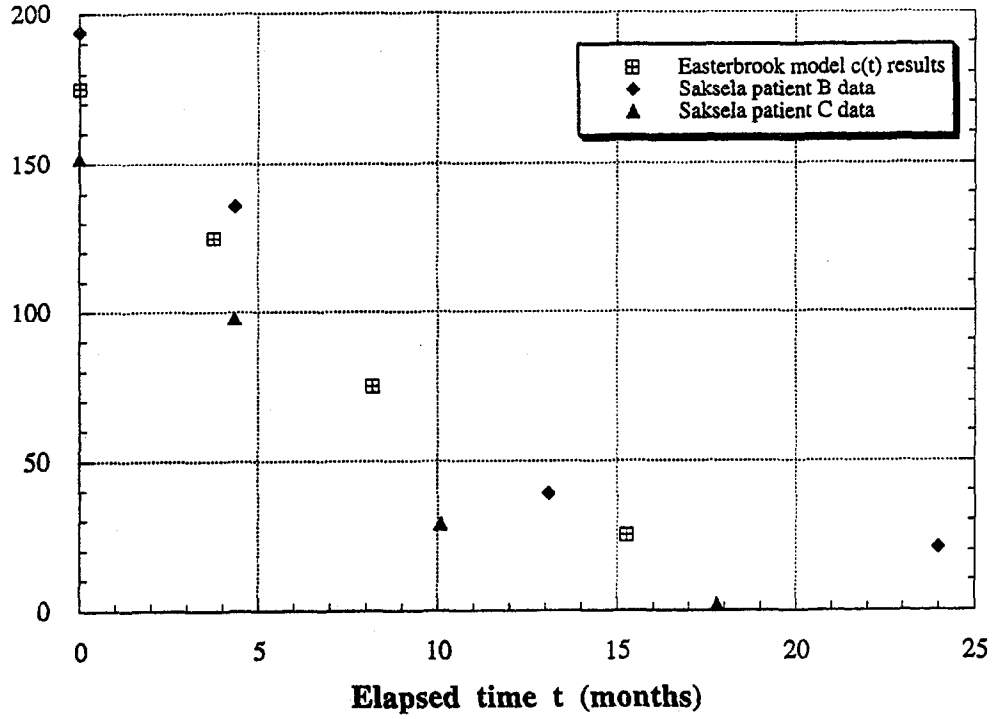
Saksela *et al.* have published data on the decline of the CD4 T-cell density in infecteds on the verge of developing clinical AIDS [11]. The CD4 T-cell densities of two of their case data (patients B and C, both receiving ZDV on a deferred basis) pass through the range of 151–200 T-cells/mm^3 on their way down towards zero. The time-dependent CD4 T-cell densities for both of these patients are plotted in Figure 2b, and the agreement with the model result is seen to be excellent. This agreement adds plausibility to the simplified model used to ascertain the bureaucratic AIDS survival curve $S(t)$ shown in Figure 2a.

The fact that the survivability of all four of the Easterbrook's CD4 T-cell subgroups can be described from a single survivability curve $S(t; 7{,}4.15\,\mathrm{m})$ has important consequences. Since the average member of the subgroup with the highest CD4 density range of 151–200 cell/mm^3 were on zidovudine therapy longer in general than the average member of the other CD4 T-cell subgroups, and since the tail end of the bureaucratic AIDS survival curve $S(t; 7{,}4.15\,\mathrm{m})$ fits the measured survivabilities of the remaining subgroups, **prolonged** zidovudine therapy *neither extends nor shortens* longevity in infecteds with bureaucratic AIDS.

Consider, for example, the survivability curve for Easterbrook's 151–200 cells/mm^3 CD4 T-cell group: $S(t; 7,\ 4.15\,\mathrm{m})$. According to the model fit, the survivability curve for those members of



(a) Comparison of Concorde, Veterans Affairs, and zidovudine (ZDV) bureaucratic AIDS survival curves.



(b) Time dependence of the CD4 T-cell density in HIV infecteds.

Figure 2.

this CD4 T-cell group who are alive at $t = t_{0\text{–}50} = 15.3$ months is identical to the survivability curve for those in the 0–50 cells/mm^3 group. Since the average surviving member of the former group has undergone zidovudine therapy 15.3 months longer than the average member of the

latter group, the fact that the survivability curves for these two groups are virtually identical implies that the *duration* of this therapy is *not* an important factor in influencing survivability. Although the duration of zidovudine therapy may not be important in determining survivability with the HIV infection, it is reasonable to assume that some minimal period of treatment is necessary to receive its benefits. Since the first data point on Easterbrook's survivability curves is 12 months, the minimal treatment period to receive all of the survival benefits of zidovudine therapy must be less than, **and may be very much less than**, 12 months. Thus, it can be inferred that all of the survival benefits of zidovudine accrue within the first year of therapy. These conclusions will now be shown to fit those of other studies.

It is instructive to compare the model results for the zidovudine bureaucratic AIDS survivability curve shown in Figure 2a with the survival curves obtained by the Veterans Affairs [5] and Concorde [6] zidovudine studies. The survivability curves for the "immediate" and "deferred" subgroups in the Veterans Affairs and Concorde studies are all shown in Figure 2a. The narrow differences between the "immediate" and "deferred" subgroup survivabilities in both studies lead the leaders of both studies to conclude that the **length of time** an average infected receives zidovudine therapy is not an important factor in influencing longevity, a conclusion that was already reached here from the model analysis of the Easterbrook data.

The relative time dependence of the three survivability curves shown in Figure 2a can easily be understood from an analysis of the CD4 T-cell density distribution of the three cohorts. Phenomenological fits to the Veterans Affairs and Concorde deferred subgroup data using the parametized function in equation (1) are also shown in Figure 2a; these survivability curves are $S_{\mathrm{VA}}(t; 5,\ 8.78\,\mathrm{m})$ and $S_{\mathrm{CON}}(t; 1,\ 95.9\,\mathrm{m})$, respectively. The range in baseline CD4 densities of the Easterbrook (bureaucratic AIDS), Veterans Affairs, and Concorde cohorts are 151–200 cells/mm^3, 200–500 cells/mm^3, and unrestricted, respectively. Thus, the Easterbrook cohort not only had the lowest baseline mean CD4 T-cell density of the three cohorts in Figure 2a, but was also the one with the narrowest distribution. Since the CD4 T-cell density is a good surrogate marker of disease progression, this hierarchy of baseline CD4 T-cell density distributions accounts for the fact that the survival curve of the bureaucratic AIDS cohort declines first and has the steepest descent while that of the Concorde cohort begins its decline last and has the mildest rate of decline.

Easterbrook *et al.* also compiled survivability data for subgroups characterized by different CD4 T-cell density ranges below 50 cells/mm^3; these results are shown in the bottom half of Table 1 and are plotted in Figure 3. Phenomenological fits to data for three of these subgroups using the parametized function in equation (1) are also shown in Figure 3. The survivability curves obtained from the fit for each of these subgroups turned out to be $S_{31\text{–}40}(t; 3,\ 4.84\,\mathrm{m})$, $S_{21\text{–}30}(t; 2,\ 5.60\,\mathrm{m})$, and $S_{0\text{–}10}(t; 0,\ 15.2\,\mathrm{m})$. It is clear from these curves that the survivability with zidovudine therapy is a very sensitive function of the CD4 T-cell density below 50 cells/mm^3.

The survival curve for those on zidovudine therapy during 1990–1991 whose CD4 T-cell density fell below 10 cells/mm^3 resembles that of the 1985 Maryland clinical AIDS survival curve, also shown in Figure 3. The gap between the latter two survivability curves is only 2–4 months, a difference that could have nothing to do with zidovudine therapy but could be due to the improvement in the treatment of the opportunistic infections characteristic of AIDS. Thus, whatever benefit zidovudine therapy has in increasing survivability above 10 CD4 T-cells/mm^3, it appears to be ineffectual below this density. Thus, three important conclusions can be drawn from the model analysis of the Easterbrook data.

First, zidovudine therapy is incapable of preventing death in those with progressive HIV disease, a conclusion drawn from the survivability curve for Easterbrook's 0–10 CD4 T-cells/mm^3 group in Figure 3.

Second, within the error of the model fit to the Easterbrook subgroup survivability data, **prolonged** zidovudine therapy neither extends nor shortens survivability in infecteds with bureaucratic AIDS.

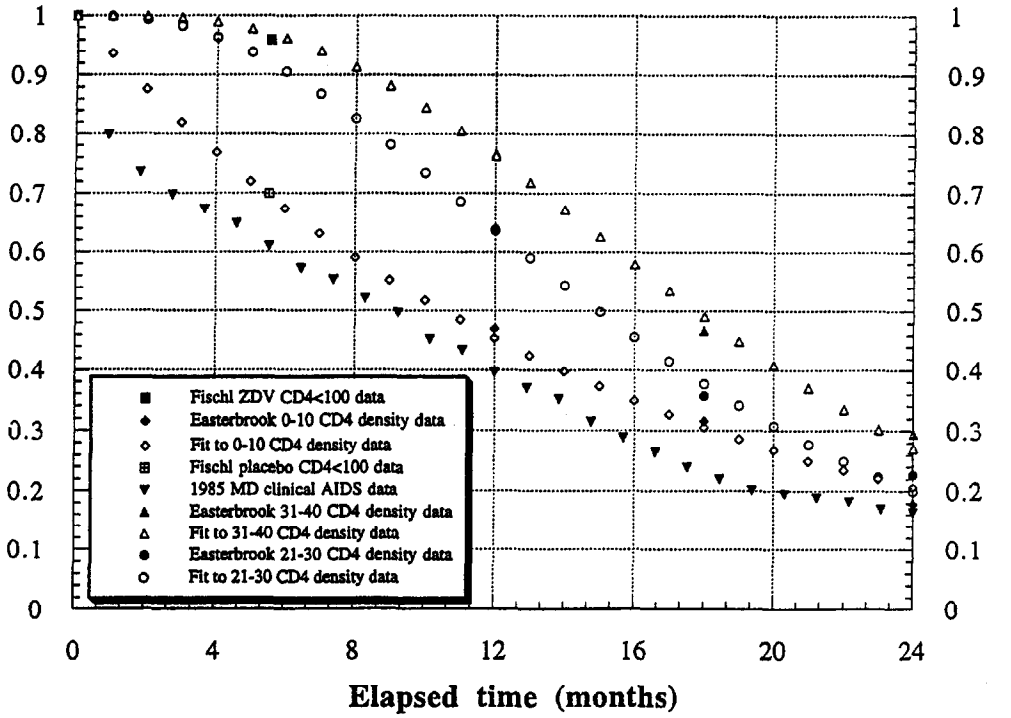


Figure 3. Comparison of zidovudine (ZDV) survival fraction data of Easterbrook and Fischl.

Third, any increase in survivability stemming from zidovudine therapy accrues within the first year of treatment and actually may accrue within a much shorter period of time.

These results collectively suggest that the effectiveness of zidovudine therapy diminishes with time and may be ineffectual after a certain treatment period; if this is true, then zidovudine therapy can eventually be discontinued without influencing survivability. Since zidovudine therapy is expensive and is generally associated with more side effects [12], there are added reasons to directly test the important possibility that **prolonged** zidovudine therapy is unnecessary.

Since all the subjects in the Easterbrook study were receiving zidovudine therapy, the impact of zidovudine therapy on survivability cannot be quantified from this study except to say that it is obviously limited. Since the efficacy of zidovudine therapy in extending survivability appears to be independent of the stage of HIV infection in infecteds whose CD4 densities fall below 200 cells/mm^3, zidovudine therapy should be initiated when the infection reaches a potentially fatal stage in an infected, administered for the limited period of time during which it is effective (to be determined from experiment), and then *discontinued.*

To quantify the impact of zidovudine therapy on survivability, it is necessary to consider double-blind controlled experiments with zidovudine and placebo receiving HIV-infected groups followed into the late stages of the disease; this leads us to an analysis of the 1986 study of Fischl *et al.* [1].

ANALYSIS OF THE FISCHL ZIDOVUDINE EFFICACY RESULTS

The survivability data of Fischl *et al.* [1] stratified by CD4 T-cell density most closely parallels that of Easterbrook. Fischl projects that the 24-week survival for subjects with CD4 T-cell densities $\leq$ 100 cells/mm^3 are 0.96 for the zidovudine treatment group and 0.70 for the placebo group, data that are plotted in Figure 3.

As seen in Figure 3, Fischl's single point on the zidovudine survivability curve for subjects with CD4 T-cell densities $\leq$ 100 cells/mm^3 falls between Easterbrook's $S_{21\text{–}30}(t; 2, 5.60\,\text{m})$ and $S_{31\text{–}40}$ $(t; 3, 4.84\,\text{m})$ survivability curves. Considering that the CD4 T-cell densities of Fischl's subjects spanned the entire range of 0–100 cells/mm^3 while the two Easterbrook groups spanned

the restricted ranges of 21–30 cells/mm^3 and 31–40 cells/mm^3, these results are consistent with each other. Thus, this Fischl point is plausible.

Interestingly, Fischl's single point on the survivability curve for the placebo subjects with CD4 T-cell densities $\leq$ 100 cells/mm^3 falls on Easterbrook's zidovudine $S_{0\text{–}10}(t; 0,\ 15.2\,\text{m})$ survival curve. Since the latter curve is a slightly shifted version of the non-zidovudine effected 1985 Maryland clinical AIDS survival curve, this Fischl point is also plausible.

The procedure used to model the survivability curve for the Easterbrook data given in the top half of Table 1 will now be used to calculate the survivability curve for HIV infecteds whose CD4 T-cell densities drops below 40 cells/mm^3.

Modelling the data for the last four Easterbrook subgroups listed in the bottom half of the Table 1 as was previously done with the data in the top half, a simultaneous fit to all the survivability data was sought using 3 independent "lag" times t_i as parameters and the 2-parameter function in equation (1) to represent the survivability curve. The data and the best fit to it are shown in Figure 4. The fit is obviously very good and has a norm of residuals of 8.7%. The survivability curve $S_{40}(t;\ n, t_p)$ for infecteds whose CD4 T-cell density just drops below 40 cells/mm^3 is best represented by choosing $n = 3$ and $t_p = 4.86$ months in equation (1). The "lag" times for each of the indicated CD4 T-cell subgroups generated by the fit turned out to be $t_{21\text{–}30} = 2.88$ months, $t_{11\text{–}20} = 3.85$ months, and $t_{0\text{–}10} = 5.52$ months. A major result of this model is that it enables the calculation of the survivability curve 5.5 months **beyond** Easterbrook's experimental range of 24 months, as seen in Figure 3.

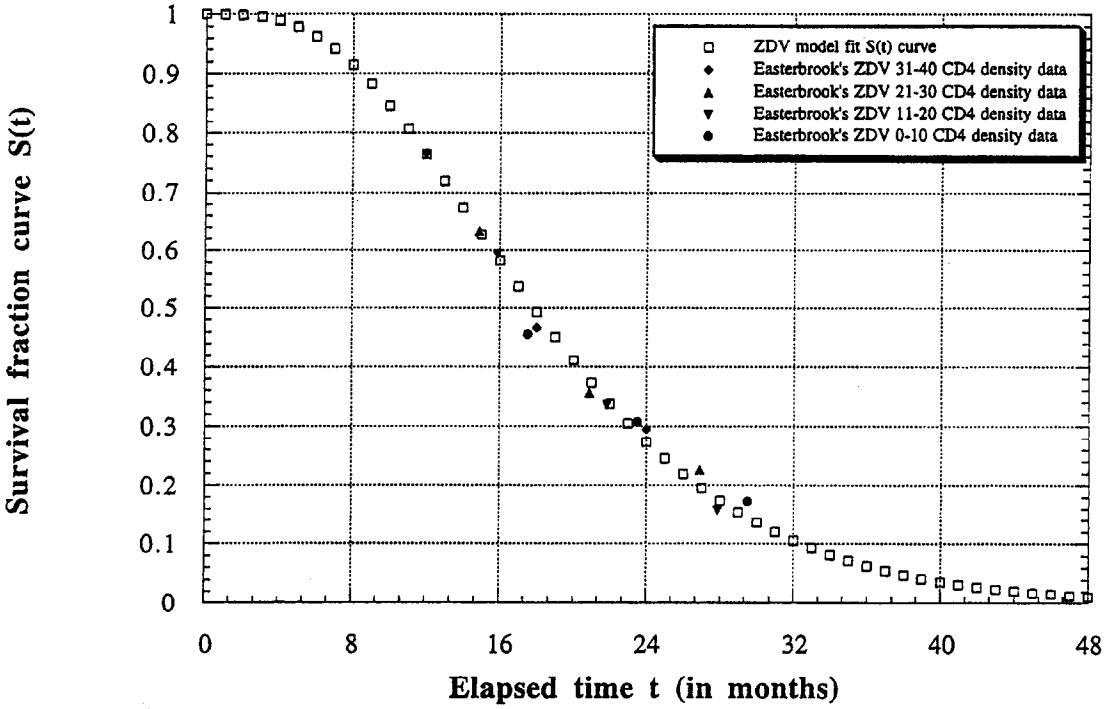


Figure 4. Survival curve for zidovudine (ZDV) treated patients with CD4 T-cell densities in the 31–40 cells/mm^3 range.

Since Fischl's two respective survivability data points for its zidovudine-receiving and placebo groups essentially lie on the survivability curves for Easterbrook's 31–40 cell/mm^3 and 0–10 cell/mm^3 zidovudine-receiving groups, respectively, and **assuming future points on the two Fischl survivability curves will continue to lie on these respective Easterbrook curves**, then the $t_{0\text{–}10}$ lag time implies that the survivability curve for Fischl's zidovudine-receiving group lags 5.5 months behind that of Fischl's placebo-receiving group. Thus, this analysis suggests that zidovudine therapy may extend survivability of HIV infecteds by perhaps

Table 2. CD4 density time-dependence of patients with AIDS (Fischl data [1]).

Time (weeks)	AZT Group			Placebo Group		
	Patients Tested	Median Density (cells/mm^3)	Mean Density (cells/mm^3)	Patients Tested	Median Density (cells/mm^3)	Mean Density (cells/mm^3)
Baseline	85	54.0	65.6	75	49.0	77.0
4	69	133.0	151.6	68	38.5	68.8
8	72	96.0	123.4	60	43.1	64.4
12	67	68.0	105.7	56	32.7	55.8
16	44	49.0	81.0	36	29.0	60.2
20	25	49.0	64.7	14	32.0	47.3
24	8	18.5	36.6	5	20.0	34.0

5.5 months on the average but does not prevent death. This conclusion is supported by time-dependent CD4 T-cell density data for Fischl's zidovudine and placebo receiving groups. The time-dependent CD4 T-cell density for Fischl's subjects with clinical AIDS is reproduced in Table 2 here for convenience (see [1, Table 4]). Sometime within the first 8 weeks of the initiation of zidovudine therapy the mean CD4 T-cell density of this subgroup increases to a maximum value and then subsequently **drops** monotonically. By contrast, the mean CD4 T-cell density of the placebo-receiving subgroup continues to drop almost monotonically. By the end of 24 weeks of zidovudine therapy, the CD4 T-cell densities of the zidovudine subgroup are virtually indistinguishable from the placebo receiving subgroup! If the CD4 T-cell density is a surrogate marker of survivability, then those surviving 24 weeks of either zidovudine or placebo therapy will have identical subsequent survivabilities!

It is interesting to note that Fischl *et al.* terminated their study at 24 weeks, precisely the point at which the survivability curve for their zidovudine-receiving subgroup is expected to begin sharply declining, as seen in Figure 4. By ending their study early, Fischl *et al.* missed the fact that zidovudine therapy has a limited ability to influence survivability for those with progressive HIV disease.

DISCUSSION

It is important to point out a *possibly* serious flaw in the controls of the 1987 Fischl, 1992 Veterans Affairs, and 1994 Concorde studies arising from the 1994 discovery by Hogg *et al.* that lower socioeconomic status is associated with shorter survivability following HIV infection [13]. Specifically, Hogg found that HIV infected Canadians whose income was below the poverty line have a more rapidly declining survivability curve than infecteds whose income was above the poverty line. This disparity occurred in spite of the low-income group being younger on the average than the high-income group. After adjustment for age, Hogg found that lower income men had a 60% higher mortality risk than high income men. The study was controlled for baseline CD4 T-cell density, subsequent use of anti-virals and prophylaxis against *Pneumocystis carinii* pneumonia, number of visits attended during follow-up, and the access and quality of medical care (all study members used the **same** set of selected family practitioners in a country that has universal health care).

Thus, for example, if Fischl's zidovudine group had a significantly lower income than Fischl's control group, then at least part of the disparity in survivabilities recorded between these two groups would be due to factors having nothing to do with zidovudine.

Lest the Hogg result for the HIV infection be viewed as an aberration, it is worthwhile pointing out that links between a lower socioeconomic status and higher rates of morbidity and mortality have been established for cardiovascular diseases and various cancers [14].

An important study of the impact of zidovudine therapy on viral load in HIV infecteds was conducted by Loveday *et al.* [15]. Loveday recruited 11 HIV infected homosexual men in 1992 with CDC group IV disease who were beginning zidovudine therapy and who could have their blood frequently sampled. The authors found four stages of effectiveness to zidovudine therapy as described below.

In the first stage, the HIV-1 load in the average subject sharply dropped to a minimum value of about 10–20% of its baseline value within an average of 7 days after beginning zidovudine therapy.

In the second stage, the viral load of the average subject sharply **increased** until it reached 40–50% of its baseline value. The second stage ends within weeks of beginning zidovudine therapy.

In the third stage, the viral load continues to increase monotonically but at much slower rate than in the second stage. This stage can last for months.

In the fourth and last stage, when zidovudine therapy is discontinued, the viral load sharply returns to its baseline value.

It is important to notice that the viral load in the peripheral blood does **not** drop to vanishing values at any time after the initiation of zidovudine therapy. The fact that after about a week of the beginning of zidovudine therapy the viral load in the peripheral blood of an HIV infected person sharply rebounds suggests that the HIV infection resumes its progression by the beginning of the second stage. Saksela *et al.* [11] have shown that viral replication in peripheral blood mononuclear cells is a predictor of forthcoming accelerated disease progression reflected by a precipitous drop in the CD4 T-cell density from normal values towards zero. Since detectable viral replication in the peripheral blood at the end of a prolonged incubation period is an indication that the HIV infection is approaching its potentially fatal stage, zidovudine therapy buys some time but does not end the accelerated progression of the disease. Using the results of the analysis of the Fischl data, zidovudine therapy may be viewed as causing the HIV infection to regress to a previous stage of the disease, one that the infection passed through perhaps 5.5 months before on the average, but the progression of the infection then resumes and follows a course similar to one uninfluenced by zidovudine.

The Loveday results can be viewed through the prism of quasi-static equilibrium dynamics between HIV and CD4 T-cells. In the advanced stage of the HIV infection, the production rate of virions and CD4 T-cells are approximately equal (actually, the HIV production rate is probably slightly higher than that of the CD4 T-cells). The drop in the viral load in the peripheral blood after zidovudine therapy is initiated (stage one) suggests that the HIV production rate drops **below** that of the CD4 T-cells in this stage. However, the infection regains its footing, and the HIV production rate again overtakes that of the CD4 T-cells by the end of the first stage (one week of therapy!). In the second and subsequent stages of zidovudine therapy, HIV outproduces the CD4 T-cells. Since the viral load apparently does not rebound to its baseline value as long as zidovudine is administered, remaining around 50% of its baseline value in the third stage (but nonetheless increasing), and since zidovudine eventually loses its ability to impact survivability, viral load is not a good surrogate marker of survivability. Moreover, if a baseline viral load and one of, say, 50% of this value yield virtually the same survivability, then zidovudine therapy becomes ineffectual in the third stage after a few months of treatment, and zidovudine therapy can be safely stopped thereafter without jeopardizing longevity.

The inability of zidovudine therapy to *prevent infection* after exposure to HIV is described in a report by Lange *et al.* [16]. In a tragic hospital accident, a seronegative 58-year-old heterosexual man was injected with HIV-contaminated blood. This mistake was realized within minutes of its occurrence, and within 45 minutes after exposure to HIV-1, massive zidovudine therapy was begun. In spite of the daily administration of large amounts of zidovudine, the patient

seroconverted on the 41st day after exposure. These results suggest that the HIV-1 infection could be established by cell-to-cell transmission of the virus [17] or that zidovudine may not completely inhibit reverse transcription [18]. The latter explanation could account for the limited ability of zidovudine therapy to stop HIV replication *in vivo* and extend the survivability of HIV infecteds with bureaucratic AIDS.

REFERENCES

1. M.A. Fischl, D.D. Richman, M.H. Grieco *et al.*, The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex: A double-blind, placebo-controlled trial, *N. Engl. J. Med.* **317**, 185–191 (1987).
2. M.A. Fischl, D.D. Richman, N. Hansen *et al.*, The safety and efficacy of zidovudine (AZT) in the treatment of mildly symptomatic human immunodeficiency virus type 1 (HIV) infection: A double-blind, placebo-controlled trial, *Ann. Intern. Med.* **112**, 727–737 (1990).
3. P.A. Volberding, S.W. Lagakos, M.A. Koch *et al.*, Zidovudine in asymptomatic human immunodeficiency virus infection: A controlled trial in persons with fewer that 500 CD4-positive cells per cubic millimeter, *N. Eng. J. Med.* **322**, 941–949 (1990).
4. R.D. Moore, J. Hidalgo, B.W. Sugland and R.E. Chaisson, Zidovudine and the natural history of the Acquired Immunodeficiency Syndrome, *N. Eng. J. Med.* **326** (7), 437–443 (1991).
5. J.D. Hamilton, P.M. Hartigan, M.S. Simberkoff *et al.*, A controlled trial of early versus late treatment with zidovudine in symptomatic human immunodeficiency virus infection, Results of the Veterans Affairs Cooperative Study, *N. Eng. J. Med.* **326** (7), 437–443.
6. M. Seligmann, D.A. Warrell *et al.*, Concorde: MRC/ANRS randomized double-blind controlled trail of immediate and deferred zidovudine in symptom-free HIV infection, *Lancet* **343**, 871–881 (April 9, 1994).
7. P.J. Easterbrook, J. Emami, G. Moyle and B.G. Gazzard, Progressive CD4 cell depletion and death in zidovudine-treated patients, *JAIDS* **6** (8) (1993).
8. M. Narro, New definition of AIDS arrives, bringing new concerns, *New York Times*, B3 (January 6, 1993).
9. R.A. Royce and W. Winkelstein, Jr., HIV infection, cigarette smoking and CD4+ T-lymphocyte counts: Preliminary results from the San Francisco Men's Health Study, *AIDS* **4** (4), 327–333 (1990).
10. I. Kramer, Is AIDS an invariably fatal disease?: A model analysis of AIDS survival curves, *Mathl. Comput. Modelling* **15** (9), 1–19 (1991).
11. K. Saksela, C. Stevens, P. Rubinstein and D. Baltimore, Human immunodeficiency virus type 1 mRNA expression in peripheral blood cells predicts disease progression independently of the numbers of CD4+ lymphocytes, *Proc. Natl. Acad. Sci. USA* **91**, 1104–1108 (February 1994).
12. W.R. Lenderking, R.D. Gelber, D.J. Cotton, B.F. Cole, A. Goldhirsch, P.A. Volberding, M.A. Testa (for the AIDS Clinical Trials Group), Evaluation of the quality of life associated with zidovudine treatment in asymptomatic human immunodeficiency virus infection, *N. Eng. J. Med.* **330**, 738–743 (1994).
13. R.S. Hogg, S.A. Strathdee, K.J.P. Craib, M.V. O'Shaughnessy, J.S.G. Montaner and M.T. Schechter, Lower socioeconomic status and shorter survival following HIV infection, *Lancet* **344**, 1120–1124 (1994).
14. R.G. Wilkinson, Income distribution and life expectancy, *BMJ* **304**, 165–168 (1992).
15. C. Loveday, S. Kaye, M. Tenant-Flowers, M. Semple, U. Ayliffe, I.V.D. Weller and R.S. Tedder, HIV-1 RNA serum-load and resistant viral genotypes during early zidovudine therapy, *Lancet* **345**, 820–824 (1995).
16. J.M.A. Lange, C.A.B. Boucher, C.E.M. Hollak, E.H.H. Wiltink, P. Reiss, E.A. Van Royen, M. Roos, S. Danner and J. Goudsmit, Failure of zidovudine prophylaxis after accidental exposure to HIV-1, *N. Engl. J. Med.* **322**, 1375–1377 (1990).
17. P. Gupta, R. Balachandran, M. Ho, A. Enrico and C. Rinaldo, Cell-to-cell transmission of human immunodeficiency virus type 1 in the presence of azidothymidine and neutralizing antibody, *J. Virol.* **63**, 2361–2365 (1989).
18. M.S. Smith, E.L. Brian and J.S. Pagano, Resumption of virus production after human immunodeficiency virus infection of T lymphocytes in the presence of azidothymidine, *J. Virol.* **61**, 3769–3773 (1987).