

Review of AZT multicenter trial data

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The approval of AZT as a treatment for AIDS was based on the results of a single multicenter placebo controlled trial, the results of which were reported in the *New England Journal of Medicine* (NEMJ) of July 23, 1987. The most important efficacy parameter claimed for AZT was a reduction in mortality in AIDS and advanced ARC patients who received the drug compared to the patients receiving placebo. Additional efficacy parameters that purported to show benefits of AZT included a reduction in the occurrence of opportunistic infections (OIs), and increases in the numbers of T4 lymphocytes.

The study entered 281 patients (144 AZT, 137 placebo) in 12 centers across the country. Enrolment took place over a period between February and June 1986, and was planned to last for 24 weeks. However, on the recommendation of an independent Data Safety and Monitoring Board (DSMB) in September 1986, the placebo arm of the trial was discontinued because mortality was virtually confined to this group compared to those receiving AZT. Because of its premature termination, only 15 individuals completed the planned 24 weeks and 27 (9.5%) completed 23 weeks. The mean time on the study was close to 120 days in both placebo and AZT recipients. Nineteen patients who did not receive AZT died compared to only one AZT recipient by the time the study was terminated.

The differences in mortality appear dramatic. However, since the efficacy of AZT was measured against deaths in the group receiving placebo, it is important to know what the causes and circumstances of these deaths were and that survival in the group receiving AZT can be reasonably attributed to an effect of the drug that could not have been achieved by any less toxic means.

What were the causes of death?

137 patients received placebo; 75 had AIDS, and 62 had ARC. The 75 AIDS patients had all experienced a first episode of *Pneumocystis carinii* pneumonia (PCP) within three months of entry into the trial. Seven of the 62 ARC patients on placebo died, and 12 of the 75 AIDS patients on placebo died. Almost all the deaths occurred within 20 weeks of entry into the trial. Thus, 16% of AIDS patients died earlier than 8 months after their first episode of PCP.

It is stated in both the *NEJM* report and the FDA reviews that a check was made at the termination of the study to determine survival. Of the 19 placebo deaths, 9 occurred in patients who had withdrawn from the study (8 to 111 days before death).

It appears that the causes of death were not properly documented. For example, one patient died at home of "AIDS." There was no autopsy. There were four PCP and three unspecified pneumonia deaths. One individual died of pulmonary edema with suspected MAI. The FDA reviewers' written report states:

On the case report forms for the patients who died, there are only a few which report biopsy or culture proof of the clinical diagnosis reported. No actual histology, pathology or culture reports are attached. The reported causes of death are listed by the sponsor in Table 3.1-3.

The causes of death reported to the FDA are listed in Table 1, below. As can be seen, they do in fact differ from the causes of death published in the *NEJM* report.

TABLE 1

Reported to FDA (Also in Appendix A)		New England Journal of Medicine	
PCP	4	PCP	8
Toxoplasmosis	2	Toxoplasmosis	2
Cryptococcosis	2	Cryptococcosis	2
MAI	2	MAI	4
CMV	1	CMV	1
Lymphoma	1	Lymphoma	1
"AIDS"	1		
Pneumonia (unspecified)	3	Wasting	1
Pulmonary edema	1		
Suspected MAI, TB or CMV	2		

It is clear that the causes of death were not properly established. The important question of whether any of these deaths might have been preventable, at least within the duration of the study, is therefore more difficult to approach.

PCP Deaths

Eight PCP deaths were reported in the NEJM article, but only 4 were reported in the FDA review. Perhaps the 3 unspecified pneumonia cases and the 1 pulmonary edema case were assumed to have been PCP, as these are missing from the NEJM report. This is of course impossible to determine, but raises the question of whether antemortem attempts at diagnosis were made by bronchoscopy in these 4 patients and whether they were in fact treated for PCP. In fact it should be determined if and how all of the 8 PCP patients were treated.

Toxoplasmosis and Cryptococcosis Deaths

In the FDA review, the following information can be found regarding the 4 patients with cryptococcosis and toxoplasmosis. Two were entered as ARC and died 3 weeks later. Both were enrolled at the same center. One, with less than 100 T4 cells at entry died on day 10 of "possible cryptococcosis." The other, with 230 T4 cells at entry died on day 21 of biopsy proven toxoplasmosis. How long before death was the brain biopsy performed in this relatively healthier patient (with more than 200 T4 cells)? A third patient who had been diagnosed 5 days after entry died of cerebral toxoplasmosis on day 39.

Toxoplasmosis is treatable, as is cryptococcosis, although probably not curable in the setting of AIDS. How were these four patients treated?

MAI Deaths

It has been said that MAI infection is not treatable in AIDS. However, there is no uniform agreement on this issue, and it is realistic to believe that life may be prolonged in patients with MAI by treatments that include ansamycin and clofazamine.

Were any of the patients with MAI treated?

There is no information on how these patients were treated, let alone information on how the diagnoses were documented. It is therefore impossible to ascertain if any of the above reported deaths might have been preventable, at least within the duration of the study, by means less toxic than AZT.

It is entirely possible that a structured program of patient management might have prolonged the lives of these patients. A structured program of patient management means a formal plan of patient supervision, which includes attempts to diagnose and treat opportunistic infections at the earliest time, as well as the provision of general supportive care.¹

There certainly was no uniformity regarding patient management within a given center, let alone between centers. Discretion on the issue of patient management was left to individual physicians.² The FDA reviews contain the following statement relating to this matter:

No standard work-up of symptoms/ signs suggestive of an OI was specified in the protocol. Thus, the aggressiveness with which patients were worked up for suspected or possible infection was left to the discretion of the investigators.

If general patient management can make an impact on survival, then could there be any reason to believe that management of patients might have differed between the placebo and AZT groups? There is at least one theoretical consideration that indicates that such differences could have occurred. This is that observer, and to some extent, patient bias could have influenced management, and thus outcome. Bias could have operated because blinding of patient and observer cannot be regarded as having been reliable with respect to who received placebo or active drug. The purpose of blinding is to ensure that bias will not be introduced by such knowledge of which participants are receiving active drug or placebo.

With regard to the patient, at the start of the trial the capsules of AZT and placebo were distinguishable by taste. This was corrected at some point, but when is not mentioned. With respect to the observer, no attempt was made to "white out" values on the routine blood count that are affected by AZT, and that would therefore indicate that an individual was probably receiving the drug. This is particularly true for the mean corpuscular volume (MCV) which is affected by AZT as early as two weeks. The FDA reviews note the following:

Statistically significant increases from baseline red cell mean corpuscular volume (MCV) were noted in AZT-treated patients beginning in the second week of treatment.

This does not, of course, mean that the investigators actively looked for changes in the routine blood counts that would indicate that a particular patient was receiving AZT; it merely notes that the purpose of blinding was not met, and bias could have influenced the outcome of the trial in that patients known to have been on AZT may have been treated differently from those who received placebo. That the treatment groups may have unblinded themselves is acknowledged by the FDA reviewer in a section concerning potential biases in the OI data, and the lack of a standard workup of signs or symptoms suggestive of an OI (discussed above).

With randomization performed by center as well as by high/low T4 count at entry, this lack of standardization may not have introduced significant bias, but the fact that the treatment groups unblinded themselves early could have resulted in bias in the workup of patients.

This means that the efficacy of AZT may be better or worse than actually reported. For example, with respect to the effect of AZT in reducing the frequency of opportunistic infections, if OIs were sought more aggressively in AZT recipients compared to patients receiving placebo, and were still found less frequently, this would suggest an even greater benefit of AZT than reported. On the other hand, with respect to AZT's effect in increasing survival, bias could also have resulted in a more aggressive treatment of AZT patients with a presumed or diagnosed OI compared to placebo recipients. This could result in an improved survival of the AZT group which would be incorrectly attributed to an effect of the drug.

The *NEJM* report states that survival was increased in patients on AZT, with T4 cell numbers below 100 as well as those with counts above 100. However, there is no mention that the increased survival was not apparent if a value of 200 T4 cells is used to discriminate between two groups of patients. This analysis comparing the outcomes in patients who had more or less than 200 T4 cells at entry was requested by the FDA and reported on. It is demonstrated that survival increases are not seen in patients with more than 200 T4 cells at entry because there was only one death in the first few weeks in this group during the period of observation. The reviewer states that the analysis does not demonstrate that AZT is ineffective in increasing survival in this group of patients (with more than 200 T4 cells at entry), but reflects the fact that there were too few patients in this category and only one death. However, it underscores the fact that the trial did not provide evidence for an effect on survival in this group of patients, and no statistically significant effect on the occurrence of OIs as well. The justification for the use of a toxic drug in this relatively healthier group of patients remains in question.

With regard to the duration of the effect reported on survival, there is now no way to adequately measure this as the placebo subjects were all offered AZT in September 1986. By December 1986 there were 7 deaths and 11 by February 1987 in the AZT recipients (those originally on AZT). It is clear that the risks of OIs and death increase after 18 weeks of treatment, but there is no control group with which to compare the patients who have been receiving treatment. In view of its toxicity and particularly the possibility of cumulative toxicity, the administration of AZT beyond 16 weeks may not be justified with the information currently available.

Other than antiretroviral effects, could the increased survival reported in the original study be attributed to an effect of AZT that might be achieved by a less toxic intervention?

The *NEJM* report raises the possibility that AZT might exert an effect by a direct antimicrobial action on opportunistic pathogens, only to dismiss this as unlikely.

However, AZT does inhibit the Epstein-Barr virus (EBV), at concentrations that are not too different from those reported to inhibit HIV. However, the methods of testing for activity against these two viruses must be very different and comparisons of inhibitory concentrations are probably impossible.

However, the possibility that some inhibition of EBV by AZT occurs cannot be discounted with the information presented. (According to the methods reported, compared to HIV, EBV inhibition requires about a 10-20 times greater amount of AZT in vitro, but as mentioned, comparisons are difficult because virus growth must be measured in different ways).

There now is considerable evidence that indicates that reactivated EBV infections are common in AIDS and ARC, and indeed, from the outset of the epidemic it has been suggested by some that active EBV infections contribute to the pathogenesis of AIDS (1,2). Acyclovir is considerably less toxic than AZT, and if any of AZT's benefits result from an effect on EBV, this fact should be established as a matter of urgency. Patients who received acyclovir in addition to AZT were reported as having an even more favorable outcome. This has been attributed to a synergistic action of AZT and acyclovir on HIV replication. However, the possibility that benefits result from inhibition of EBV seems just as likely as both drugs inhibit EBV. A trial of high dose acyclovir alone may demonstrate an efficacy equal to that reported for AZT, without the marrow suppressive effects of the latter drug.

AZT interestingly also had an inhibitory effect against giardia, which suggests that effects directly against *Pneumocystis* may exist. It was reported that this was not so, but the extent to which this was investigated was not mentioned. However, if there is an anti-pneumocystis effect of AZT, it cannot be too powerful, as AZT does not prevent this infection. AZT is also highly active against a group of gram negative bacteria, including salmonella, and shigella, although there is no reason to believe that this activity was of clinical benefit(3).

With respect to the claimed improvements in T4 cell numbers in AZT recipients, the rise that is reported in the AIDS group was not sustained. In these patients, the T4 count begins to drop at 12 weeks and at 28 weeks is actually less than it was at entry. In the ARC group there is also no substantial change in T4 cell numbers. There is a realistic possibility mentioned by one reviewer that with time, AZT may inhibit T-lymphocyte as well as red blood cell and neutrophil precursors; this may be of some consideration in patients whose disease depletes them of T-lymphocytes and have taken AZT beyond 12

weeks.

Toxicity of AZT

The FDA Reviews also contain information suggesting that the toxicity of AZT has been underreported.

Because so many of the AIDS-related signs and symptoms could also be adverse drug experiences, it is difficult to determine whether these events are actually disease-related or drug-related. It seems that the bias towards reporting them as one or the other (which likely varied among investigators) was altered during the course of the study from a 'bias' towards 'overreporting' them as possible adverse drug events at the beginning of the study, to 'overreporting' them as presumptively disease-associated events later in the study.

Further, the following circumstance was noted with varying frequency:

Adverse experiences were sometimes crossed out months after initially recorded, even though 'possibly related to test agent' had been checked off originally by the investigator or his designee. Perhaps this was done at the same time the symptom sheets were transcribed, with the assumption that symptoms should not also be recorded as adverse events. In any case, this type of action typifies the confusion concerning the appropriate way to record symptoms and possible adverse reactions, and casts some doubt on the validity of the analyses of these parameters.

It is clear that AIDS patients manifest a wide variety of symptoms and that some understandable difficulty will exist in attributing symptoms to AIDS or to an adverse reaction to AZT. One way to obtain information on this point that was pointed out in the FDA reviews was to compare adverse experiences between AZT and placebo recipients among patients with ARC who had less disease-related symptoms. Such a comparison was indeed made, and it was noted that in ARC and high T-4 patients (essentially the same patients), an adverse effect was reported more frequently in the AZT recipients compared to placebo. This seems to indicate that adverse drug-related experiences in AIDS and low T4 patients could have been masked.

A further problem in the assessment of adverse AZT responses is the fact that only patients who were ambulatory and kept their scheduled appointments contributed data.

If patients experienced adverse reactions requiring hospitalization, or received medical attention at other locations, the details were likely to be slow in reaching the Case Report Forms for this study.

There is no record of the number of missed visits.

Subsequent to the approval of AZT, a considerable marrow toxicity of this agent has been shown in an assay that could possibly have been done before the study(4). Inhibitory effects were shown on blood precursor cells by concentrations of AZT readily achievable at the dosage used in the study.

Furthermore, in a letter to the *NEJM*(5), Dr. Seymour Cohen questions, in connection with the toxicity of AZT,

which normal cells are severely damaged? Is the damage reversible or irreversible? Are the cells killed and the chromosomes fragmented, as one might expect from a termination of DNA chains? Are AZT and ddC mutagenic, or possibly carcinogenic? These questions have not yet been answered, to my knowledge.

The response to this letter(6) indicated that AZT can, in fact, induce chromosomal abnormalities in

human lymphocytes, and does have some mutagenic effects in mouse lymphocytes. The FDA reviews also contain comments on possible carcinogenicity and chromosomal aberrations related to AZT. In the FDA reviews it is stated that AZT does inhibit cellular DNA synthesis (to a lesser extent than reverse transcriptase), and that its triphosphate can also be incorporated into DNA, which then terminates chain elongation.

Another factor that could have contributed to the increased survival of the AZT recipients compared to those receiving placebo is the possible life-prolonging effect of blood transfusions in patients with AIDS. Dr. Yoritaro Inada and Dr. Michael Lange of St. Luke's-Roosevelt Hospital Center (New York) have been studying the therapeutic effect of blood transfusions in AIDS. The basis for this study is the well-established fact that individuals with AIDS and ARC have circulating immune complexes (CICs) frequently at high levels, and that an important mechanism for clearing these abnormal components is defective in AIDS and ARC patients. This mechanism is the ability of red blood cells to bind CICs to receptors on their surface, and the transport of the bound CICs to the liver where they are degraded.

In AIDS and ARC patients, the receptors are saturated and CICs accumulate in the serum. Dr. Inada has demonstrated that the transfusion of red blood cells from healthy donors is followed by reductions in the levels of CICs in the recipients, and a therapeutic effect may be associated with this phenomenon. This procedure requires that donor blood be screened to ensure that the red blood cells have receptor activity, as it has been found that only about two-thirds of donated blood units in blood banks have such activity.

Dr. Inada and Dr. Lange are continuing their study of the therapeutic effects of blood transfusions in AIDS supported by a grant from the American Foundation for AIDS Research. In the AZT trial, 46% of AZT recipients who had AIDS were transfused frequently and repeatedly, compared to 15% of the placebos. If two thirds of these units were able to reduce the levels of CICs, and if such effects are life-prolonging, the transfusions may indeed have made some contribution to survival.

Conclusion

In conclusion, the use of AZT, a drug of considerable toxicity, has been justified predominantly on the finding that survival was longer over a sixteen week period in AZT recipients compared to controls receiving placebo. The survival statistics are not in question. It is the interpretation that AZT was responsible for the observation (by virtue of its antiretroviral action) that must remain in doubt for the following reasons:

- 1. It is likely that the ways in which patients are managed can make an impact on survival;**
- 2. There was no uniform program of patient management within centers, let alone between centers; and**
- 3. There is a realistic possibility of patient and observer bias and such bias could have influenced patient management.**

Factors other than an anti-HIV effect also may have contributed to the increased survival of the AZT recipients. These include an anti-EBV action of AZT, as well as some contribution from the blood transfusions received by many AZT recipients. In addition, even if the increased survival was due to AZT, this benefit is less demonstrable after 16 weeks and the toxicity can be expected to become more apparent with time.

The toxicity of AZT is probably greater than reported, and it can be expected that reports will continue to appear demonstrating deleterious effects of the drug. Therefore, the administration of AZT should probably be limited to 16-20 weeks, and until there are study results, there is no justification for its use in groups other than that in which a survival benefit was claimed, that is, in patients with fewer than 200 T4 cells.

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1:Attempts at preventing PCP will hopefully be included in future protocols, even while waiting for data establishing the efficacy of PCP prophylaxis in AIDS (particularly with aerosolized pentamidine).

2:It is surprising that no comparison of mortality between centers was provided (as well as comparisons of other outcomes between centers).