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Comment on the [AZT article](#) posted in the Contents section.

This is certainly not a history of the introduction of AZT. There are many such histories, written from different points of view; several can be found on the internet simply by searching "AZT History".

My article concerns the trial on which its approval was based. As far as I know, my article and a review written by John Lauritsen, are the only two that were written at the time AZT was approved, and based on the FDA's review of the manufacturer's report. Of course there have been many later reviews of this trial. John Lauritsen has written several accounts of problems he found in reviewing the trial. (<http://www.amazon.com/Poison-Prescription-Story-John-Lauritsen/dp/0943742064>

<http://www.virusmyth.com/aids/hiv/jltrial.htm>).

There are points of agreement, but the emphases do definitely differ. I most certainly do not think that the remarkable reported results of the trial can be attributed to intentional fraud. I do not believe that the excess mortality seen in the placebo arm is in question; it is not a fiction resulting from improper reporting, or improper randomization of sicker patients to receive placebo. But it cannot be ruled out that bias influenced the way patients were managed, and at that time, the single most important influence on mortality was the nature of patient management. Essentially, patients died mostly from opportunistic infections. These are often preventable, and treatable. Prevention and treatment are aspects of patient management, the nature of which can make the difference between life and death. The reasons that bias could have influenced patient management are discussed in the article, essentially it could have resulted from unblinding of the trial. It is important to state that we cannot know in which direction bias influenced physician practice. But it is only possible to conclude that the placebo recipients and the AZT recipients may have been managed differently - but not which group received better or worse care.

I reviewed the report both as a primary care provider to people with AIDS, and thus challenged very aggressively, both by my colleagues and by many patient advocates, to actually prescribe AZT. I also reviewed the report as a clinical researcher who had designed and implemented clinical trial protocols.

I learned a great deal – in both these capacities. The most important thing I learned was that contrary to the defeatist attitude so prevalent at the time, there was in fact a great deal that we could do for our patients. While we had no life saving intervention, we were able to extend the lives of our patients by attending to the opportunistic infections. The development of aggressive patient management strategies had been neglected. The denial of PCP prophylaxis for so many years is maybe the most dramatic example. But we might have thought about prophylaxis of other opportunistic infections earlier. We might have thought of measures to be taken to enable early diagnoses to be made, and improve our treatments. The Public Health Service might have issued guidelines well before the 1989 recommendations for PCP prophylaxis, regarding patient management strategies. To give just one example: if a patient is known to have a positive test for toxoplasmosis, the subsequent development of a cerebral lesion would in some instances be diagnosed more

rapidly and successfully treated even sometimes without the need for hospitalization. In New York, San Francisco and Los Angeles it is likely that many physicians soon learned to test all their new patients for toxoplasmosis, but I rather think this was less common elsewhere. With survival extended by careful patient management strategies, more of our patients would have survived to receive the benefits of potent antiretroviral therapies. It is entirely possible that high dose AZT monotherapy, added to the neglect of general patient management and made this possibility less likely for some. Dr Samuel Broder, the Head of the National Cancer Institute actually stated that the introduction of AZT made PCP prophylaxis less important.

The introduction of AZT as the first approved treatment for HIV infection was much anticipated as a result of considerable publicity given to it well before its approval, which described its great benefits. Dr Samuel Broder who was head of the National Cancer Institute appeared on television shows trumpeting the benefits of a drug he at first refused to name and then called Compound S. I remember a TV show where he appeared with an AIDS patient who enthusiastically attested to the benefit he had derived from the drug. Knowing how this drug exerted its effects I was immediately cautious. AZT is an analogue of thymidine which is a normal building block of DNA. It is incorporated, instead of thymidine, into DNA during its synthesis, and then immediately stops further DNA chain elongation. Quite apart from its chain terminating properties, I had further concerns - both from my laboratory experience and experience as an infectious diseases physician. The use of such analogues was considered to be perilous when I first dealt with them many years ago. I had used them in the virology laboratory in experiments conducted in vitro, and they were handled with caution, as potentially hazardous substances. In clinical practice, apart from acyclovir which is a similar drug, but in a special category, such analogues were used systemically in malignancies and some viral infections - such as herpes encephalitis, but only for short periods. Acyclovir is in a different category as it can only be used by the herpes virus enzymes, and has no effect on human DNA. The idea of a possibly **lifelong** exposure to a DNA chain terminating compound - or even an analogue that is incorporated into DNA that continues to be synthesized, was I believe a novel concept at that time. To emphasize, what was novel was not the use of such compounds, but a life time exposure to them. . So, I was somewhat concerned at the very idea of this approach, and also found it strange that colleagues were mostly silent on this issue. These analogues need to undergo changes in the cell, and are added to the growing DNA chain by enzymes, either those that belong to the cell, or enzymes that are specific to the virus, such as the reverse transcriptase of HIV. It was hoped that AZT, which is turned into its active form by cellular enzymes, would be preferentially used by the viral rather than the cell enzymes that synthesize DNA, and therefore not terminate cellular DNA synthesis; there was some evidence to support this. HIV's reverse transcriptase adds AZT to the viral DNA chain, while cellular enzymes add it to cellular DNA. Cell DNA is found in two different sites. In the nucleus it is the DNA that constitutes our genome – that is all the information that determines our inherited characteristics. DNA is also found in cellular structures called mitochondria which are the

source of the energy needed by the cell. Two different enzymes are needed to make DNA in each situation. While there was comforting evidence that AZT much preferred the viral reverse transcriptase to the enzyme that makes our genomic DNA, this preference was less evident in the case of the enzyme that makes mitochondrial DNA. In fact much of the toxicity of AZT is a result of its effect on mitochondrial DNA synthesis.

The announcement of the results of the first efficacy trial of AZT conducted by Margaret Fischl was dramatic. The trial, where half the participants received the drug, and the other half were given a placebo was terminated prematurely because AZT was seen to have had such a powerful life saving effect, that all participants were offered AZT. The amazing result was that there were 19 deaths in those receiving placebo and only one in those receiving AZT. Needless to say such a dramatic effect of AZT has never been seen again.

I immediately knew there was something suspect about these extraordinary trial results for a very simple reason. I had a large practice providing care to HIV infected people, including many with similar characteristics to those taking part in the trial. Among my patients with these characteristics - including those who had recovered from Pneumocystis pneumonia, none had died within three months following their recovery. In fact, if my patients had been the trial participants, AZT would have shown absolutely no effect on mortality in a three month period. This was true not only for my practice. The trial was conducted at several centers; New York City was one. Nobody in the New York City site died. All the New York City trial participants were also the patients of several doctors in the city - so they too did not expect to see the mortality reported in the trial. At some other sites, the trial researchers were also the treating physicians. As an important digression, there is an example – a lesson, to be learned here, about the compatibility of the role of researcher and that of provider of medical care. Comparisons of the outcomes where patients care was provided by the researcher, with the outcomes where the researcher and provider of medical care were separate roles, will indicate that outcomes were worse when both roles were combined. Although, there are those who hold a different view, I believe that these roles, that of researcher, and that of care provider are incompatible in many clinical trials. But this is the subject of another article.

Returning to the bizarre trial results, at first I thought some academic researcher would investigate them and come up with an explanation. None was forthcoming, and so I reluctantly felt obliged to do this myself. Through the freedom of information act Project Inform, an advocacy group in California, obtained the FDA report on the manufacturers - Burroughs Wellcome- application for approval of AZT. Unfortunately large sections were blacked out. I therefore obtained a second copy following a request for it by Act Up, a New York activist organization. For some reason this copy was different in being almost entirely legible. I spent about 2 weeks carefully going through this report (while conducting a busy practice) and the article published on this site describes what I found and how the strange results might be explained.

It was immensely disappointing to find that many of the problems in the trial were identified by Ellen Cooper, the FDA reviewer, yet the drug was still approved at a dosage that proved to be so toxic that another trial compared a similar dose with half that dose. This exercise resulted in excess deaths among those taking the higher dose. (A randomized controlled trial of a reduced daily dose of zidovudine in patients with the Acquired Immunodeficiency Syndrome. Margaret A Fischl et al. NEJM 1990: 323:1009-14).

Among the many bizarre aspects surrounding the introduction of AZT was the claim that the excess deaths in those receiving the higher dose were due to AIDS - that in the case of AZT, less is better - the explanation given for the superiority of the low dose compared to the high dose was that the lower dose allowed people to remain on the drug for longer - not even a hint that the higher dose contributed to the increased mortality. Here is the representation of the mortality differences between the two dosages:

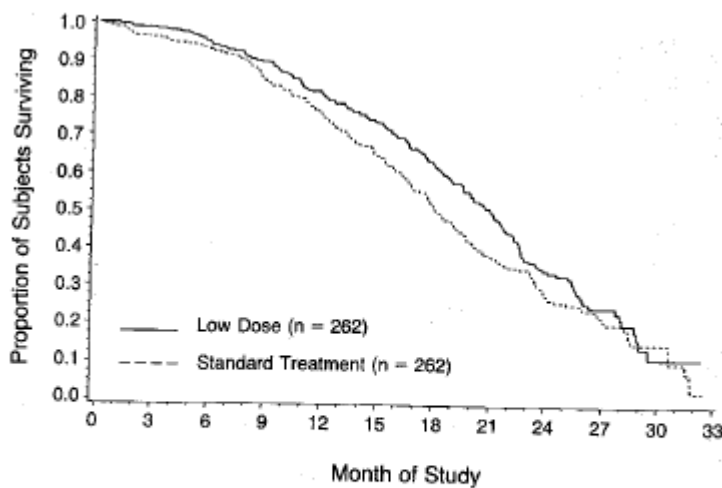


Figure 1. Estimated Distributions of Lengths of Time to Death, According to Treatment Group.

One hundred sixty-nine subjects died in the low-dose group, and 188 in the standard-dose group ($P = 0.019$ by the Wilcoxon test).

If ever evidence was needed that AZT – at the initial recommended dose of 1500mg daily probably caused an excess mortality – the figure above provides it, despite the disingenuous claims of the authors that the deaths were due to AIDS. A rational response would have been to work out the minimum effective dose. Why stop at 600mg a day? 300mg a day is probably just as good. It is the dose I prescribed with no evidence that 300mg AZT daily was associated with a worse outcome. As described in another article it is likely that endogenous interferon plays a role in pathogenesis, and AZT promptly removes it from the circulation. This is one of the leads never explored; it is probably too late to do so now as the newer antivirals also remove interferon (and some other abnormally expressed cytokines) from the circulation.

That the possibility that more people on the higher dose died from AZT toxicity is not even mentioned in the above report is a sad indication of what has become of the discussion of results section in a scientific paper, at least in the field of AIDS. Traditionally all possibilities are discussed, even to be dismissed, but not in this paper.

The publicity following the approval of AZT was huge. Doctors received a video where AZT was billed as "A ray of hope". I recall white coated doctors speaking about the "light at the end of the tunnel".

The dosage schedule was absurd, and I suspect may have been devised to create some ritual to give added prominence to this "ray of hope", as there was no scientific basis at all for four hourly dosing. AZT was to be taken even at night, and patients were given beepers to remind them to take their medicine exactly at the appointed time. AZT is not the compound that blocks HIV replication. It is changed into the active compound in the cell by the addition of phosphate, and so blood levels tell you nothing about the levels of the active form in the cell. It is also a little gruesome - because as it turned out adherence to this difficult ritual was associated with great toxicity, and I can imagine that sometimes the manifestations of this toxicity would be attributed to AIDS and patients encouraged to still keep their beeper going and continue to take AZT. At first the drug was only available if patients met certain criteria, and I know colleagues, devoted to their patients, who forged the papers to enable their patients to get the huge dose of AZT. All on the basis of approval based on a terribly flawed trial, but in reality on the marketing genius of the manufacturers. It is really awful to fight to obtain something that is almost promised to save your life, and to find that it actually may shorten it. Of course the need for some therapy was quite desperate and one must wonder if this desperation lowered the threshold of what was deemed to be acceptable, so that there was perhaps less scrutiny of the trial and the failures of AZT at the dose used – until of course toxicity forced a reconsideration of the dosage.

I never prescribed it when it was first approved, and when I did it was at a dose of 300mg a day - usually, sometimes when combined with another drug - combivir it was taken at a dose of 600mg

Because I was one of the few physicians around 1987 who did not prescribe AZT I attracted patients who were reluctant to take it and whose physicians were nor supportive of this choice. I also received severe criticism for my position, even to the extent of some claiming that I should be sued for malpractice for not advising the use of AZT. At the time, I would have welcomed the opportunity to publicly defend my position, feeling quite confident that I was sufficiently informed to do this.

This original AZT trial did however clearly demonstrate to me how important patient management strategies were in the treatment of AIDS, particularly in the days before the more potent antiviral drugs became available.

The New England Journal of medicine, which reported the original trial rejected my article reproduced in the Contents section. I sent copies to all the clinicians who were prominent in the field - as well as to several patient advocates. There was not a single response - not even to reject the points I made. Total silence. Realizing the difficulty in publishing independent material we – myself and mostly Michael Callen , decided to publish an independent journal. We called it AIDS Forum. Michael was the editor, and it lasted for three issues, but my article was published in it.

Very unfortunately, the most vocal of the critics of the AZT trial included some individuals who did not believe that HIV could cause AIDS, and I had to contend with sometimes being lumped with this group. I thought that my review of the AZT trial was actually quite conservative with its criticisms based on the traditions of clinical practice and research.

One last comment on the baneful effects of this trial: While it was not responsible for the undue influence industry has on medical practice, this trial probably provided the greatest impetus towards the sad situation we are in today. It is possible that in the field of HIV medicine, industry had its greatest opportunity to establish a firm hold on many different ways to influence practice. These include not only marketing strategies, but influence on guidelines committees, support of continuing medical education, the support of medical conferences and influence on reports of their proceedings, as well as the invention of the Key Opinion leader or KOL, to provide information to physicians. “Key Opinion Leader” is not the only absurd designation in this field. We also have “Thought Leader”. Needless to say these distinctions are not conferred by any academic institution; I would assume that the marketing departments of pharmaceutical companies are responsible for choosing who deserve these titles.

Useful references:

A history of the development of AZT with an emphasis on the interrelationship of government and industry: <http://www.scribd.com/doc/1049/The-History-of-AZT>

