
1. What was the motivation for doing this clinical trial?
What motivated this trial was when optimal treatment for HIV positive people should occur. Basically when to treat patients with drugs.

2. What was the design?
The design was to create a randomized clinical trial comparing two antiretroviral treatment strategies. The participants were not blinded to either group. The groups were a continuous antiretroviral therapy and an episodic treatment that only used the anti-HIV drugs. Review committee was also blinded.

3. What patients were eligible for this trial?
Patients were chosen as those who had current CD4 rates in excess of 350, any drug conservation or (ART) history, and willingness to start, modify or stop drug conservation treatment according to a randomized placement. They also had to be older than 13 and not pregnant or breast feeding.

4. Why is the CD4+ cell count important?
When they dropped below 250 cells per cubic millimeter treatment began and when the CD4+ count rose above 350 cells per cubic millimeter treatment stopped. These thresholds determined whether treatment began or stopped in the drug conservation (DC) group.

5. What was the primary endpoint? What was the alternative hypothesis?
The primary endpoint was the development of an opportunistic disease or death from any cause.

6. The sample size target for the trial was 6000 patients.
What was the basis for that?
The trial needed 6000 patients to have a power of 80% to detect a 17% reduction (hazard ratio .83) in opportunistic diseases or death in the drug conservation group compared to the viral suppression group. (VS) Why it was 17% was unknown to Jacque Neuhaus.

7. In the Statistics section of the Methods, it says: "Randomization was stratified according to clinical site with the use of permuted blocks of random sizes." What does this mean, and why did they do it? How many clinical sites were there? Where were they?

It means the sites did not have the same number of patients. Each “block” has equal numbers of each treatment that are randomly assigned to the patients, and it states that the blocks were of random sizes. This method could be biased if the people making selections are not blinded to the randomization. They could have more favorable patients be in the drug conservation group.

According to the results, there were 318 sites in 33 countries. The countries include: Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Israel, Italy, Japan, Lithuania, Luxembourg, Morocco, New Zealand, Norway, Peru, Poland, Portugal, Russia, South Africa, Spain, Switzerland, Thailand, United Kingdom, United States and Uruguay. Interesting how only South Africa is the only African country.

8. The Data and Safety Monitoring Board terminated this trial early. What factors went into their decision? What is your understanding of the "O'Brien-Fleming boundary and the Lan-DeMets spending function"?

The DSMB recommended stopping enrollment, as additional follow-up data would be unlikely to exhibit long-term superiority of the DC group compared to the VS group. They believed that the study be redesigned or stop it all together. The data they had at the time stated that the primary endpoint was double the rate in favor against the drug conservation group as evidenced in table 2. The O'Brien-Fleming boundary gives “boundaries” for usage that if the boundaries are crossed, the null hypothesis is rejected. In this trial, the trial was conservative early on as not many events relative to the sample size had occurred, making it an ideal test. They also set up significant levels.

Lan-Demets spending function deals with significant levels and the error for stopping the tests. Error rate is unknown for each test, but less than 5%. If the null hypothesis is true, there is a 5% chance to reject the null hypothesis in a type 1 error.

9. Do you agree with the DSMB's decision to stop early? Why or why not? What are some reasons that might be considered to continue the study longer?

I agree with the board. Obviously figure 2 gives some evidence into the belief that the drug conservation (episodic) group would likely not become superior. The safety risk was
simply too great to risk a favorable result from an unfavorable position. The outcomes were extremely inconsistent with the primary outcome as they had planned. The study could continue as Jacquie mentioned. The boundaries used were guidelines, not rules to be always strictly followed. Ethics would also have to be disregarded.

10. What does Figure 2 tell you? What does 'censored observation' mean? Figure 2 tells me that the drug conservation group is statistically worse in every category. The treatment is not always radically worse, but regardless never an improvement from viral suppression.

I searched the article online and was not able to find a, “censored observation.” I found a censored amount of data for participants that perished before January 11, 2006. Incomplete data, such as the people lost to follow up acclaims for this. The status of the event would be 0 for no event of interest, and one variable for time period.

11. What does Figure 3 tell you? Figure 3 gives me some insight on the hazard ratio difference exhibiting that the viral suppression group is better for the patient. These statistics seem misleading as the information varies in numbers of participants with events. The p-values do help to grasp the interactions of the events.

12. Do you find the results of this trial convincing? Explain. Yes. Usage of fewer drugs equals more death and additional complications, but continuous drugs mean higher toxicity levels. Toxic drugs will give negative effects, especially long usages, but not administering them can lead to a rather certain death.

13. Do you think it is likely that the results of this trial will change clinical practice? Yes. It will give insight into the usage of anti-viral drugs that was previously postulated, not researched properly. The results are published and presented in lectures that are available to doctors that should go into usage.

14. Some people were disappointed with the results of this study. Who were those people, and why were they disappointed? The study researchers were disappointed with their results. In the editorial, Dr. Currier stated that the “higher-than-expected rate of major cardiovascular, renal, or hepatic disease in the drug conservation group” and how it exceeded predictions.

Patients in the DC group might be disappointed on the results. Poor countries would have been disappointed that the DC’s lower cost is ineffective. In addition, insurance companies and HMOs would also wish for a cheaper alternative.

15. Who sponsored this study? Why? The Division of AIDS of the National Institute of Allergy and Infectious Diseases or NIAID though a plethora of private companies gave support in one way or another such as Pfizer, Merck and Johnson & Johnson among others.
Different drugs were employed in an unusually large study that made for drug companies to doubtfully fund the study.

16. Has there been much improvement in the treatment of HIV/AIDS since the disease emerged in the early 1980s?
Yes to some degree I do agree with the obvious answer. New drugs are developed every day and time will help to treat devastating diseases. Since the virus mutates in different hosts and each individual is vastly different, I say that the treatment has not improved a considerable amount. Patients suffer the exact same symptoms as in the early 80s. Are the patients treated better? I suppose so. We know all the symptoms of HIV/AIDS and misdiagnosis is likely less than it was, but relief from the virus is ambiguous. It has not turned into a virus that people can “live” with without major complications.

17. Does the 'profit motive' play a role in medical progress? Explain.
I would like to think no, but it must. I remember a standup routine by the comedian Chris Rock on this very same question of AIDS not being cured:

“They ain't curing it, 'cause there ain't no money in the cure. The money's in the medicine. That's how you get paid, on the comeback. That's how a drug dealer makes his money, on the comeback.”

Now I found it comical at the time hearing drug companies being compared to drug dealers, but with every minute of my life being bombarded by expensive name brand drugs that will help me live my life normally, I certainly do feel as though a cure is secondary to the treatment. A vaccine only makes so much revenue until it has been unnecessary for the population. When was the last time someone in the USA had smallpox or polio? These cases become a newsworthy segment of a society long past, one of iron lungs and diseased blankets.

In short, cures do not produce revenue; treatments sure do though, and it scares me to theorize that profits determine saving lives.

18. Why is HIV/AIDS difficult to prevent and treat? Why isn't there a vaccine?
This disease is a retrovirus and adapts to each host it claims. It is extremely to teach an immune system to affect a virus that actually attacks the immune system.

19. What are the major points made in the Editorial?
The editorial is interesting in its recap of the trial. It explains the entire trial in a straightforward manner that is considerably easier to read than the trial itself. Dr. Currier tries to explain why the drug conservation group was so inferior. She does claim that the results were not wholly unexpected, but not to the level the study found. She also explains how increases of 25% of the deaths in the drug conservation group were not related to traditional HIV events and why the deaths were ambiguous to the study. She praises the usage of randomized clinical trials to evaluate new treatment strategies for HIV patients as to make antiretroviral therapy less costly and less toxic to patients.
She also suggests that a possible use of the drug conservation treatment would be to recommend it to pregnant women with CD4+ counts above 350 to possibly prevent mother to child transmission.

20. HIV/AIDS is largely preventable by behavior modification. Some people argue that individuals should be responsible for the consequences of their own behavior. Others argue that the government should shift its resources more toward prevention rather than treatment. Others argue that studies like this should be done by drug companies, not by the government. What are your views?
I believe epidemics this lasting should be funded by the government. They should be unbiased and try to remedy and find cures for an epidemic affected the global community.
AIDS is no longer transmitted via blood transfusion, but unprotected sex is still a major issue. I remember the porn industry shutting down for a month or two in 2004 on an AIDS outbreak, reinforcing the very real disease that is not just in Africa.
Prevention is really the only way to stop this disease since no cure is in immediate sight. Even the weak spot found very recently is still a ways away from a cure.
(http://news.bbc.co.uk/2/hi/health/6357287.stm) Teaching students in school the real threats of unprotected sex might be a good idea instead of solely abstinence.