

Homework #4 - due February 26, 2007

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HSEM 3010 Spring 2007 Clinical Trials Assignment 4

Answer the following for the paper of the SMART Study Group: CD4+ Count-Guided Interruption of Antiretroviral Treatment (N. Engl J. Med (2006) v. 355, pp 2283-2296). See also the Editorial, NEJM (2006) v. 355, pp 2359-2361.

1. What was the motivation for doing this clinical trial?  
Antiretroviral therapy is very costly and has adverse side effects. This clinical trial was done in order to try the optimal way to use antiretroviral therapy, which includes the benefits of the treatment while minimizing the side effects.
2. What was the design?  
This was a randomized clinical trial, but investigators and participants were aware of treatment assignments, so it was not blinded.
3. What patients were eligible for this trial?  
Patients eligible for this trial had to be infected with HIV, older than 13 years of age, not pregnant or breast-feeding, and has a CD4+ count exceeding 350 cells/ml<sup>3</sup>.
4. Why is the CD4+ cell count important?  
The CD4+ count is a blood test which determines how well the immune system is working in people who have been diagnosed with HIV. The number of CD4+ cells drops in most people infected with HIV who aren't receiving treatment. The CD4+ count helps to determine whether other infections may occur, to determine when to start antiretroviral therapy, to diagnose AIDS.
5. What was the primary endpoint?  
The primary endpoint was new or recurrent 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 designers of this study calculated that they would need 600 patients in order to have a statistical power of 80% and to detect a 17% relative reduction in the rate of opportunistic disease or death from any cause in the drug conservation group as compared with the viral suppression group.
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?  
Permuted blocks are a way of randomizing in order to promote a balance at the end of the trial between control and experimental groups. It is especially useful when there are small groups or many testing sites in order to try getting an overall balance between groups among all the sites. There were 318 clinical sites in 33 countries within North America, Europe, South America, Australia and New Zealand, Asia, and Africa.

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"?

Data showed that the DC group was definitively showing adverse effects to the experimental treatment in comparison to the VS group. Also, simulations done showed that the DC group would never come out ahead or improve in comparison to the VS group. These are two factors which went into the DSMB's decision to stop the trial early. The O'Brien-Fleming boundary and the Lan-DeMets spending function follow the data from the clinical trial and watch to see if it become too positive or too negative in one direction or the other. Thus, they set up stopping boundaries to protect the patients and the general public who may be affected by this study. The boundaries are most conservative early on and get narrower as time goes on and more data is collected.

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 do agree with the DSMB's decision to stop early because the DC group was showing definite results that the experimental treatment was in fact harming them rather than helping them. Even if over a longer period of time, data might have evened out between the two groups, it was not worth risking the lives of the people within the study. I do not see any reason why the study should have continued on longer; however, some may argue that the effects wouldn't be seen until much further along in the follow up study.

10. What does Figure 2 tell you? What does 'censored observation' mean?

Figure 2 shows that in all cases (opportunistic disease or death from any cause; death from any cause; major cardiovascular, renal, or hepatic disease; and Grade 4 adverse effects) the drug conservation group had a increasingly higher probability of event, which means that they occurred more frequently in this group when compared to the viral suppression group. Censored observation means observation with incomplete data such as from those lost to follow-up.

11. What does Figure 3 tell you?

Figure 3 shows that all subgroups, whether based on age, sex, race, or otherwise, had an increased risk of developing adverse effects as described previously when in the drug conservation group than in the viral suppression group. It shows that the viral suppression treatment is better than the drug conservation group.

12. Do you find the results of this trial convincing? Explain.

Yes, I do find the results of this trial convincing because the experimental group showed a continual increase in events and never showed any indication that it would get closer to the control group. Also, many of the events due to side effects of antiretroviral therapy occurred more in the drug conservation group, which was unexpected because they were receiving less treatment.

13. Do you think it is likely that the results of this trial will change clinical practice?

Yes, I do think it is likely that the results of this trial will change clinical practice because it shows that the best treatment for HIV is continuous antiretroviral therapy despite the cost and

adverse effects.

14. Some people were disappointed with the results of this study. Who were those people, and why were they disappointed?

I think the investigators as well as others working towards finding the most optimal way of using antiretroviral therapy were disappointed in the results because the results were completely opposite of what they hypothesized was going to happen.

15. Who sponsored this study? Why?

The study was sponsored by the Division of AIDS of the NIAID (National Institute of Allergy and Infectious Disease). This group probably sponsored this study because AIDS is an end point product of HIV and they deal with research in curing/treating these diseases. If this study showed beneficial results for treatment of HIV, it would impact AIDS as well.

16. Has there been much improvement in the treatment of HIV/AIDS since the disease emerged in the early 1980s?

Yes, there has been improvement. At first people with HIV/AIDS were treated as mutants almost and were only cared for to “aid” in the process towards death. As science has advanced and we learn more and more about the disease, we are able to help people who have it live a longer and more prosperous life.

17. Does the 'profit motive' play a role in medical progress? Explain.

Yes, I think the “profit motive” plays a role in medical progress because making money can become a goal instead of improving healthcare. On one hand drug companies give lots and lots of money towards research for new drugs that may or may not help treat diseases. On the other hand, money that originally went towards further education of practicing doctors instead goes towards paying stockholders. The focus turns towards money instead of the patients.

18. Why is HIV/AIDS difficult to prevent and treat? Why isn't there a vaccine?

HIV/AIDS is difficult to prevent and treat because there are continually new strains and also, the disease attacks our immune system, particularly the T-cells. This is also the reason why there isn't a vaccine. Vaccines use our immune system to create antibodies against a disease or illness, but since HIV/AIDS attacks/breaks down the immune system making it hard for antibodies to be created and stick around, especially with new, unknown strains presenting themselves.

19. What are the major points made in the Editorial?

The major points made in the Editorial include: the design of the trial was controversial because some argued that removing patients off treatment was hazardous in the first place, definitive finding of superiority of continuous treatment over intermittent treatment is important for the field and should strengthen current efforts to promote adherence to therapy once it has been started, results in drug conservation group exceeded predictions, increase in mortality in DC group was not clearly associated with traditional HIV-related events, the cause of more than a quarter of the deaths in DC group was unknown, and the most unexpected finding was that the rates of nonopportunistic disease and death were higher in

DC group than VS group when the DC group should have been relatively protected from events usually associated as side effects to treatment.

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 think that while HIV/AIDS is largely preventable by behavior modification it is still a very widespread and serious disease. There are babies who are born with the disease because their mothers have contracted it, therefore there is no way they could have prevented acquiring HIV/AIDS. I think the government should use its resources for both prevention and treatment so as to provide benefit and help to both those who have the ability to prevent themselves from contracting the disease to those who already have it. We should not let those people die because we've decided to focus on prevention and let them deal with their "poor" decisions. I think it is ok that the government is doing studies because HIV/AIDS has become a public health issue on a worldwide scale and drug companies alone cannot discover the "cure."