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Short communication

Innovative combination clinical trial designs/patient compliance: A community perspective

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1. Introduction

It has become clearer in the last year that clinical trials as they have been conducted in AIDS need to be reexamined. The way we approach the design of study protocols has to take into account that a number of overridingly important variables have recently changed. It has always been important to design clinical studies with three things in mind: (1) Study objectives, to have a clear set of questions you hope the trial will answer; (2) The length of the study, how many weeks will it take to provide the needed answers; (3) How do you ensure patient compliance?

Three major factors have emerged in the last year that should have a dramatic effect on these and other aspects of clinical trial design. They are the discovery of more potent compounds against the virus, the validation of viral burden assays from retrospective studies and a new understanding of the rapid turnover of HIV and of CD4 cells in patients.

These discoveries represent new challenges to researchers to quickly learn to utilize these technologies to advance our knowledge of how to treat this disease. Not to recognize the full import and to take full advantage at this point would be a serious mistake and result in potentially unnecessary suffering of patients.

First, in regards to study objectives, viral burden assays and the better understanding of T-cell tests give us a far greater ability to show the antiviral activity of new drugs and new drug combinations.

Second, in regards to the length of studies, the rapid turnover of the virus make it possible to measure antiviral activity even within hours of the administration of an inhibitor.

Third, in regards to how you ensure patient compliance, people with HIV/AIDS have for many years been out-smarting the system in the interest of their own personal health. The potency of the newer compounds and combinations, coupled with the superior knowledge and use of marker assays, present a real challenge to researchers to design clinical studies that patients would want to comply with. People with HIV/AIDS will not be good guinea pigs remaining on what they believe to be sub-standard control arms. For good reason, even the use and concept of the 'Standard of Care' control arm is quickly

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becoming a thing of the past in AIDS.

One can debate and raise some questions about what I have said here. Our knowledge in these and other aspects of AIDS will continue to evolve but we do not have the luxury of time to dot every 'i', slash every 't', and satisfy every shadow of the doubt while people in the most affected communities continue to die at an unprecedented speed.

The number of new drugs and drug combinations presents additional challenges. Could we have found out about the advantages of the AZT/3TC combination sooner than we did? I think we all would agree that we are likely to be using combo as opposed to monotherapy for most patients for the foreseeable future. There are hundreds of possible combinations just based on the currently approved antiretrovirals (AZT, ddI, ddC, d4T, etc.). When you add the experimental drugs that are already in Phase II testing (Saquinavir, MK 639, ABT 538, IL 2), the potentionally life saving or extending combinations number in the thousands. This number will grow to the tens of thousands quite rapidly when you add the next generation of protease and reverse transcriptase inhibitors. Also, all of our current knowledge of combination therapy show more of an effect by starting in treatment-naive patients, with a good combo regimen, than adding drugs over time. This is yet another way in which our slow clinical trial process is hurting patients.

With all of this in mind, and in collaboration with a number of community based treatment advocates, I have developed a rapid screening process for testing promising antiretrdviral combination regimens. The following is a master protocol, it can easily be modified to meet a variety of research needs.

2. Study design

Thirty patients, open label, non-randomized, one study regimen of three or more antiretrovirals, approved and unapproved compounds previously untested in combination.

2.1. Inclusion/exclusion criteria

CD4 count range; possibly two parallel studies;1. Antiretroviral naive >300 CD4,2. Antiretroviral experienced <300 CD4.

Viral Burden: No minimum copy number or a minimum of no more than 10 000.

3. Length of study

Ten weeks, all patients offered follow up and drug for 52 weeks.

4. Endpoints

Viral burden, CD4, CD8, % safety and toxicity

It is crucial that these screening studies be open label and non-randomized. This will rapid enrollment with patients far more willing to comply. Non-randomization, using only one combination regimen, will allow for a faster start up of studies. The protocols would be simpler, lacking some of the complexities that can greatly slow down the process. Only the companies whose drugs are being used in the particular study would have to sign contracts. There would be no placebos or complicated dosing regimens to design. This would be far less complicated and confusing to the patient as well.

I must make it perfectly clear that people with AIDS are already gaining access to multiple protease inhibitors. They are adding various combinations of AZT, ddI, ddC, d4T and 3TC and we currently have no clinical trials process to accommodate them. We have no way of getting honest data from their risk taking and people with AIDS are left with only our underground networks to share experiences.

Drug combinations for these rapid screening trials should be chosen based on in vitro synergy and additive effects. Consideration in choosing which regimens to study must also be based on which combinations people with HIV are experimenting with on their own. With the size of these studies being this small, it makes it possible to study very specific patient populations. Researchers could study how to treat patients with particular point mutations. These studies could provide much needed guidance to doctors and their

patients to develop individualised teatment strategies. This protocol might also represent a fast screening mechanism for testing alternative approaches to treating HIV/AIDS.

Drug combinations providing a great viral suppression and a great improvement in T-lymphocyte count and percentage would rapidly be put into larger (approx. 100 patients per arm) randomized, controlled Phase III studies in a comparison against other highly active combinations. All study arms must be equally attractive to potential volunteers.

One thing we have learned in AIDS is that clinical trials cannot give us definitive answers on how to treat all patients with HIV/AIDS. The data from studies provide guidance and direction to doctors and their patients. This is particularly true when we lack a fully effective magic bullet. The practice of medicine is as much an art as it is a science. We currently have the tools to be creative in the design of our clinical research. We must also provide for the use of those tools for individual patient care.

The following people have participated in the development of this master protocol: Tom Blount (AIDS Survival Project Atlanta), Richard Colvin (Committee of Ten Thousand), Dawn Averitt-Doherty (Women's Information Service and Exchange), Martin Delaney (Project Inform), Jules Levin, (ACT UP/NY), John James (AIDS Treatment News) and Brie Salzman (people With AIDS Coalition New York).