

National AIDS Treatment Advocacy Project

AIDS Clinical Trials Group (ACTG) Meeting of December 1996 in Washington, D.C.--Summary of Proceedings

Reported by Jules Levin

There was considerable discussion of the current state of knowledge regarding virus activity in "compartments" other than peripheral blood, such as in semen, CSF, the brain, lymph tissue, etc; and, where research may be headed in trying to better understand their relationship to potent antiretroviral therapy. Following is a discussion of some of the proceedings at the ACTG meeting, including the status of ACTG studies both ongoing or in development.

ACTG 320. Scott Hammer reported 1100 enrolled in study; accrual has slowed and some patients have withdrawn; the total enrollment goal of 1700 is overpowered and he expects to be able to enroll 1400 by reaching out for international enrollment.

ACTG 355, START Protocol-Strategic Timing of Antiretroviral Therapy Trial. Michael Saag is the PI and leading the way in trying to implement this trial concept, although it is meeting a series of obstacles.

In its current formulation, it is a phase III comparative, open-label factorial design study of antiretroviral naive subjects with CD4 counts >100 and plasma RNA > 10,000. However, changes in protocol may still occur, as revisionist discussions are actively ongoing.

2,000 study participants would be randomized to one of two treatment strategies and within each treatment strategy to one of two utilizations of protease inhibitors (immediate vs delayed).

Strategy A --"Loose Control"- less aggressive RNA load control (HIV RNA <5,000) and immediate vs delayed protease inhibitor (PI) therapy.

Vs Strategy B-- "Tight Control"- aggressive RNA load control (HIV RNA ,< 200) and delayed vs immediate PI therapy.

REGIMENS

Strategy A: "Loose Control" Group (target RNA <5,000)

Arm A1: Loose Control/delayed PI Group

Arm A2: Loose Control/immediate PI Group

Strategy B: "Tight Control" (target viral load <200)

Arm B1: Tight Control/delayed PI Group

Arm B2: Tight Control/immediate PI Group

The primary objectives are "to determine the necessity of suppressing plasma HIV RNA

to undetectable levels (<200) vs less aggressive intervention (maintaining RNA <5,000) and to determine if less aggressive therapy will yield equally positive clinical outcomes with less toxicity and costs, with comparable resistance development; and, to determine if there are any differences in outcome within each approach based on timing of use of PIs (early vs delayed)". Arms A1 and B1 (delayed PI regimens) would be initially offered 1 of 6 different regimens. Whether participants could choose or would be randomized is now open to discussion. Saag's protocol calls for patient choice; arms A1 and B1 (delayed PI) : AZT/3TC, AZT/3TC/NVP, ddI/d4T, d4T/3TC, AZT/ddI/NVP, or AZT/1592. After failure, patients would move to the next round which would consist of one of two different regimens; the next round would also consist of a variety of mostly non-protease 3-drug regimens; the final round would consist of PI- containing regimens.

Arms A2 and B2 (immediate PI regimens) would consist of 7 regimens all of which contain one of four PIs: SQV, IDV, NFV, or RTN--SQV/AZT/3TC, SQV/ddI/d4T, IDV/AZT/3TC, IDV/ddI/d4T, RTN/AZT/3TC, RTN/ddI/d4T. Following would be three potential rounds of regimen changes (all 3-drug regimens) which culminates in regimens containing two PIs.

There is much controversy surrounding this protocol, bringing into question whether or not it will get started anytime soon or at all. At the ACTG Executive Committee meeting, many objections were raised to particular protocol points; but, at the end of the session when Principal Investigators were polled, all were in favor of this concept.

ACTG 347. Phase II study of 141W94 monotherapy vs 141W94 plus AZT/3TC. 84 study participants (CD4 >50-- RNA 5,000-50,000) randomized, double-blinded, and stratified by naive vs experienced. 1200 mg bid of 141 plus 300 mg bid AZT will be used. Purpose is to look at safety, tolerability and perhaps most importantly, the potential for 141 as a mono-therapy treatment.

141W94 has been said to be in vitro more potent than other available protease inhibitors, thus its potential use as monotherapy. This may be the only opportunity to examine its potential as monotherapy over the course of this 6-month study. Tight cross-over controls have been promised by investigators for the protection of study participants--Roy Gulick and Robert Murphy. Any participant rising above level of detection of RNA assay will be offered triple therapy including 141.

ACTU Site Performance. At the Executive Committee meeting, a number of points were discussed regarding the performance of sites. 16/30 sites had at least one deficiency; one site had 3 deficiencies and 14 sites were slow in reporting a/e; the expected standard for reporting a/e is 100% in one week. Regarding study accrual, 13 sites were below mean. Strict monitoring of performance will be enforced and some of the criteria considered will be: speed of data reporting, error rate, diversity of protocols implemented, work of junior investigators, number of junior investigators. Four sites were singled out for top scientific work: Harvard, Johns Hopkins, UCSF, Northwestern. Sites were singled out for high performance in accrual: UCSF, Puerto Rico, Colorado, Penn, Seattle, Texas-Galveston. Increased efficiencies are needed; for example, sites having an immunology lab should be doing immunology studies. Tom Merigan said that the ACTG moves too slowly in implementing studies. This message was repeatedly heard

by me throughout the ACTG meeting.

Plasma RNA. The ACTG and the FDA are discussing and examining more progressive ways to use RNA in studies. Some would say this process is moving too slowly, while others would say adequate progress is being made. Scott Hammer gave a wide-ranging talk of the pluses and minuses of using RNA as a study endpoint. He concluded we need to further assess data from completed and ongoing studies, but that we were headed towards more progressive uses of plasma RNA. There were a number of presentations about using RNA in different ways as markers in studies; some of the different ways could be: actual decreases, proportion below level of detection, time to failure, AUC of RNA change minus baseline; another analysis of 175 was presented, which indicated that CD4 % was a useful marker.

IL-2. Joseph Kovacs, of the NIH, presented a discussion on the data and information to-date regarding IL-2 therapy, current plans and the needs for future planning. He presented the recently published results of an intermittent IV IL-2 study. This controlled, randomized study examined individuals with mean CD4 of about 425 and RNA of 40,000. Thirty-one individuals received IL-2 and 29 were in control group; approved nucleosides were utilized and the starting regimen of IL-2 was 18 million units per day continuously infused for 5 days intermittently.

After 10 months of study CD4 peaked at about 1000 CD4. All were offered IL-2 and were followed for at least another four months. During the course of the study, doses were lowered and regimens were individualized for tolerability and maintenance if CD4 increases. There were no sustained rises in viral load when antiretroviral therapy was used, although drugs of moderate benefit were all that was available. Study indicated adverse events and toxicities could be better managed by individualizing IL-2 regimens. The length of dosing cycles were in some instances able to be shortened from 5 days to 3 days and that lessened side effects while maintaining CD4 increases. Lesser frequency of cycles of drug still allowed for maintenance of CD4 increases.

There were 5 AIDS-defining events in the control group--1 in the first 14 months and 4 subsequent; there were 2 in the group originally randomized to IL-2 during the first 14 months and 1 subsequent. Kovacs said, some patients have been safely receiving IL-2 for 5 years in NIH open studies and still maintaining CD4 increases.

A randomized study, of individuals with higher CD4, was conducted comparing sub-cutaneous IL-2 of 7.5 million units twice per day vs a lower dose of 1.5 million units twice per day, both intermittent dosing. Although, dosing was either every month or every other month, no difference was detected between these two methods. Over the course of 6-month study period there was a slight CD4 increase in the lower dose regimen; those using 7.5 million dose experienced a 95% increase in CD4 above baseline at 6 months; 80-90% have experienced a 50% or greater increase in CD4; sub-cutaneous administration is associated with lower toxicities.

An important study conducted by Judy Falloon, of the NIH, examined 10 individuals with CD4 about 100 or lower (9/10 had CD4 below 100) receiving IL-2 therapy and potent antiretroviral therapy. Indinavir and accompanying nucleosides were permitted to

be used in this loosely controlled study. After 12 months of study, Falloon reported 7/10 participants had sustained significant rises in CD4. By my observations of the data, the individual CD4 increases experienced are at least suggestive that IL-2 can be effective in raising CD4 for individuals concurrently using IL-2 with HAART (highly active antiretroviral therapy). Kovacs, Falloon, Cliff Lane and others have concluded similarly because ACTG 328 will examine individuals with CD4 50-300 receiving either intermittent IV IL-2 or intermittent sub-cutaneous 7.5 million units per day with HAART. This phase II study is intended to address the aforementioned question of whether or not IL-2 can be effective in raising CD4 when used along with HAART, in a lower CD4 population.

Kovacs said, " for patients with early disease, we feel we have a safe and well-tolerated effective regimen. The big question needed to be answered is the clinical benefit of IL-2. For advanced disease....the Falloon data suggest efficacy." Kovacs suggested following a result of positive data from ACTG 328, a study of clinical benefit in this population should be conducted. In the plenary session as well as in the committee meeting of the IBT/RAC (Immune-based Therapy/Research Agenda Comm), I expressed strong support for moving along quickly to implement studies of clinical efficacy. It was reported by the NIH, at this committee meeting, that they are trying to put together the backing for such a study, which would be costly. Discussions are ongoing with international groups expressing desire to participate in study.

However, it will be difficult to implement this study. Normally the manufacturer of a drug financially supports such a study. In this case, it appears as though Chiron is not willing to lend full financial support to such a study. Alternative financing will be very difficult and time consuming to arrange.

Finally, Kovacs briefly addressed the question of functionality of the CD4 cells induced by IL-2 therapy. He suggested, as well as Cliff Lane has suggested, there is no data suggesting that these CD4 are not functional. He characterized the CD4 as "a polyclonal increase in both naive and memory phenotype cells.....In patients who have lost the ability to respond to recall antigens such as tetanus toxoid, IL-2 therapy does not restore that response; but, if you immunize those patients with tetanus toxoid, you are in fact able to induce an immune response...In fact, the CD4 cells in these patients are functional and are able to mount an appropriate response to challenge with tetanus toxoid following immunization....The only way to determine whether or not the CD4 cells induced by IL-2 are truly functional at the clinical level (able to prevent the development of opportunistic infections and malignancies--that's the bottom line of how we want to measure the functionality of these cells) is through a randomized phase III trial of clinical endpoints. We don't have surrogate markers, at this point, which will tell us if these CD4 increases will prevent OIs".

Commentary: As you all know many individuals are at home experimenting with the use of IL-2 obtained from their personal physicians; as well, many of us are desperate to know if IL-2 therapy can in fact have clinical benefit for advanced disease when used along with HAART; I fall into the latter category. It is imperative that we quickly launch studies to explore the clinical benefit of IL-2 in both less advanced and more advanced disease populations. Otherwise, we may never be able to truly assess this therapy. Studies

of both groups should be implemented approximately at the same time. As well, a well-designed clinical-oriented study in the advanced population could yield results relatively quickly as compared to the study in a less advanced population, which could make it much less costly in terms of both financial and human resources.

Perinatal Transmission. I wasn't able to attend any meetings addressing this subject, but it appeared from the agenda as though there will be a good number of progressive studies on the drawing board utilizing the latest potent therapy advances, finally. It was mentioned at the ACTG meeting that because Downstate in Brooklyn, N.Y. was defunded as a site, gynecological studies in general were not recruiting well because of the major contribution Downstate made to the overall recruitment of these studies.

Pediatrics. It appears to me as though there are some important advances finally being made for the pediatrics populations. Agouron has a good tasting pediatric formulation in study since June. As well, an additional peds trial is being discussed for the ACTG. ACTG 338 will randomize 240 kids (ages 2-17) between AZT/3TC, RTN/AZT/3TC and d4T/RTN. The 48-week study is expected to begin in about 4 weeks with continuation of drug upon study completion. This study will be for less advanced children and a study for more advanced children will follow. Andrew Wiznia, a study co-chair from Bronx-Lebanon, described a unique study design, in that it will allow for folding into the study additional treatment arms over the entire course of the trial. At completion, all the different treatment arms will be compared. The adults should consider getting so creative. As well, a full panel of immune markers will be examined including memory and naive cells.

One ACTG study utilizing 1592U89 has already started or will very soon begin. Another is slated to begin by March 1997. A pharmacokinetics (PK) study is expected to be conducted for neonates examining treatment intervention both within 72 hours of birth and within 21-28 days of birth. A single dose PK study has started or is about to start, examining 4 dose levels for children aged 5-13. Further peds trials are planned using 141W94. As well, Abbott is suggesting a range of different types of studies for peds including protease-protease combinations.

Protease Failures. A very important study: Dr. Roy Gulick, of NYU, and the ACTG, are planning ACTG 359 which will explore options for these individuals. It will be a mid-sized, multi-center pilot trial expected to begin by the end of the 1st quarter of 97. Discussions are ongoing about 3-drug combinations utilizing the new saquinavir formulation (enhanced oral formulation), nelfinavir, delavirdine, and ritonavir. Study participants will probably be stratified by CD4 count and viral load.

ACTG 333. Preliminary data is expected to be available in 1st QTR 1997. This is first protease inhibitor cross-resistance study; study participants with at least 1 year saquinavir experience were randomized to either the saquinavir EOF (new enhanced oral formulation with higher bioavailability) or indinavir; parameters of resistance and cross-resistance are being explored.