

TAKE THE BLINDERS OFF AIDS RESEARCH

TO DATE the National Institutes of Health (NIH) has tested no non-pharmaceutical or holistic treatments for AIDS even though many PWA's AND PEOPLE WITH HIV INFECTION REGULARLY USE SUCH TREATMENTS TO MAINTAIN THEIR HEALTH. WHY HAVE THE AIDS CLINICAL TRIAL GROUPS (ACTG's) BEEN SO BLIND TO ALTERNATIVE TREATMENTS?

- o Most alternative treatments are not developed within the established pharmaceutical industry. THE ACTG's ONLY TEST TREATMENTS SPONSORED BY PROFIT-MAKING PHARMACEUTICAL COMPANIES.

- o The NIH, in tandem with the American Medical Association, has a history of racial and cultural exclusion. MANY ALTERNATIVE SYSTEMS OF HEALING COME DIRECTLY FROM THE COMMUNITIES WHICH THE WESTERN MEDICAL MODEL HAS TRIED SO HARD TO SUPPRESS.

- o ACTG protocols require that all subjects be treated alike. Women and people of color do not necessarily react the same to the same treatment, and have thus often been restricted from clinical trials. BECAUSE HOLISTIC SYSTEMS TREAT EACH SUBJECT AS AN INDIVIDUAL. TESTING PROTOCOLS FOR SUCH THERAPIES ARE DESIGNED ALONG BROAD-BASED PRINCIPLES FOR THE SPECIFIC SUBJECT. HOLISTIC TREATMENTS DO NOT EXCLUDE GROUPS OF PEOPLE.

- o ACTG protocols most often require hard data exit points. i.e. death, as a means of judging a treatment's effectiveness. HOLISTIC TREATMENTS REGARD THE QUALITY OF LIFE LIVED AS A MORE INFORMATIVE TYPE OF EVIDENCE OF A TREATMENT'S EFFICACY.

- o ACTG protocols have focused primarily on HIV. In doing so prophylactic treatments and immune-modulators have been ignored. MOST ALTERNATIVE AND HOLISTIC TREATMENTS LOOK AT THE ENTIRE HUMAN SYSTEM RATHER THAN AN INDIVIDUAL VIRUS. THEY ARE FOUNDED ON THE PRINCIPLE THAT A STRONG IMMUNE SYSTEM IS THE BEST DEFENSE AGAINST OPPORTUNISTIC INFECTIONS AND AIDS.

- o Most substances treated by the ACTG are developed in a test-tube, which often has little relation to the human body. MOST ALTERNATIVE TREATMENTS ARE DEVELOPED THROUGH EXPERIENCE IN HUMANS. THE FACT OF THE TREATMENT WORKING IS MORE IMPORTANT THAN THE AGENT OF ACTION.

- o In the spirit of scientific chauvinism, ACTG's do not accept evidence from outside the United States. MANY ALTERNATIVE NON-PHARMACEUTICAL TREATMENTS WERE DEVELOPED AND HAVE BEEN TESTED WITH ENCOURAGING RESULTS OUTSIDE OF THE U.S.

WE DEMAND

1. That the ACTG initiate unbiased investigations of alternative treatments for AIDS such as vitamin and nutritional supplements, herbs and plant derivatives, as well as alternative established healing systems such as acupuncture and homeopathy.
2. That the ACTG relax overly restrictive protocol requirements so that clinical trials of treatments based on alternative models of health and disease can be conducted.
3. That the ACTG accept data from community-based trials as well as from international studies, to determine the efficacy of treatments.
4. That the ACTG stop focusing on anti-HIV drugs and include studies of treatments which bolster the immune system and improve the quality of people's lives.

**DISMISSAL OF ALTERNATIVE TREATMENTS
WITHOUT UNBIASED TRIALS IS UNSCIENTIFIC!**

END MICROBIOLOGICAL MYOPIA



The AIDS Coalition to Unleash Power NY

AIDS CLINICAL TRIAL GROUP MEETING

APRIL 1992

ACT-UP GOLDEN GATE

TREATMENT ISSUES COMMITTEE

REPORTBACKS

PEDATRICS - Vince Maloney

NEUROLOGY - Matt Chappell

TB & OTHER OI's - Matt Sharp

ONCOLOGY & CCG - Andy Zysman

WOMEN'S ISSUES & MISC. - Virg. E. Parks

REPORT ON 14th ACTG: PEDIATRICS
by Vince Maloney

Issues in Pediatrics

1. Infants

- 20% have rapid progression and die before age 2
- accurate early diagnosis is difficult

2. Perinatal transmission

- about 30% of HIV+ women transmit to the fetus
- transmission seems to be intrapartum (during labor & delivery) rather than intrauterine

3. Opportunistic infections

- PCP is most common
- peak of PCP is between 3 & 5 mos. when diagnosis is difficult
- no clear plan for ped TB intervention; need for coordination with adult TB researchers (who apparently aren't interested)

4. Vaccines

- vaccine trials in children should start in 6-9 mos.

5. Some protocols and questions

- 051-why the deaths (1/5) ?
- 170-is this necessary?
- 182-is this ethical?
- 185-when, oh when will it start?

1. Primary Therapy-to develop 5 template protocols

Phase II/III

- few as 2, as many as 4 arms
- if patient's condition is deteriorating, she would qualify for a salvage protocol, not this

Phase I/II

1A

novel anti-retro-virals for the first time; pharmacokinetic (PK) studies; 1-3 sites; to determine acute toxicities; evaluate PK profile; determine if age-related differences exist; determine dosage for 1B-C

1B-C

toxicity and PK for drugs given over a period of time; determine dosage levels for Phase II/III; get in vivo resistance

Salvage

- for very sick children
- may use Phase II/III entry criteria i.e., if children fail II/III, they qualify for salvage
- LIP would be one entry criteria, as well as other OIs

Placebo-controlled early therapy (asymptomatic)

- waiting for 182 (AZT v placebo in asymptomatic infants under 9 mos.)
- if patient reaches endpoint on 182, she is off study, regardless of which arm she is on

Management

- late treatment management
- for children on therapy more than a year and doing well
- large simple trial
- infrequent evaluations
- which treatment is better, as opposed to asking questions about toxicity, virology, etc.

2. Obstetrics/Pediatrics

076 (AZT v placebo in pregnant women and infants)

- accural is now 748 mothers, about 10 per week
- adverse reactions were evenly distributed by treatment group and were normal pregnancy complications, not drug-related
- infants born to IVDU mothers had lower neutrophil counts
- NIAID Communications Office (301-496-4000) has a summary of 076

other perinatal protocols and issues will be included later

3. Opportunistic Infection

LIP and parotitis more common in children; KS and lymphoma less so
PCP most frequent, esp. between 3 & 5 mos; 20-30% of infants allergic to Septra-alternate agents must be researched

HIV infection results in blunted to absent antibody response; therefore, passive replacement therapy with IVIG is logical

CMV- PK of oral gancyclovir needs to be defined

Varicella-vaccine is anticipated in 1 year; IV acyclovir the current treatment

MAI- 178 (Phase I Clarithro PK study); considering a Phase I study of Rifabutin (note: Adria has said that a liquid formulation of Rifabutin is ready, and will be going into a trial in June.)

Measles- severe and often fatal

Working Group is piloting a device called a capsule, intended to expedite research (see Appendix 1). These would be submitted before concept sheets, and should facilitate early approval, and implementation, of Ped OI trials. If successful, they will be used throughout pediatrics.

4. Vaccine

Yale study of gp160 in children

I did not go to the Vaccine WG meeting because of a conflict

5. Immunology

Goals

Immunologic assays, interruption of perinatal transmission, and immunologic staging of HIV in children

5. Immunology-cont'd

Problem-blood samples are often limited

Newborn immune system

Low levels of all complement components

Decreased activity of all pathways

Immune function (opsonic) defects in infants under 200 gms

Neonatal monocyte function

monocyte numbers normal

viral killing reduced

low IgG in premature infants;absent IgA

Newborn's t-cells partly intact,partly deficient;abnormal regulatory system;poor cytotoxic function; t-cells extremely labile (unstable).

Cytokines,etc.

IL2 all T-cells

IFN- γ memory t-cells

IL4 memory t-cells,stimulates IgE

TNF α monocytes, memory b-cells

T-cell proliferative response - best way to assess function
correlation with skin tests

Methods for assessing proliferative response

3 T uptake

flow cytometry

IL2 synthesis

DNA analysis-cycling

Superantigen-microbial antigen capable of directly activating t-cells by
binding to a specific region of the t-cell receptor

How to get at the question of CD4 depletion vs poor synthesis?

In first 3-6 mos.,CD4s are much higher than in adults

CD38 developmental and activating marker good for CD8, not so good
for CD19

CD19s required for pediatrics

Th Response by cord blood cells to PHA:100%
Th Response by CBL to ALLO:75%
Th Response by CBL to Flu:0%
Th Response by HIV peptide:58%

Function more predictive of HIV status than markers

Info which argues against in utero exposure

Viremia at 3-5 mos resolves without anti-retroviral therapy

6. Virology

To determine if resistance to anti-retrovirals develops more rapidly in children than in adults

7. Neurology/Psychology

Neuro/Psych endpoints must be included as an endpoint in Ph II/III anti-retroviral protocols

Working Group will develop standardized way to evaluate neuro/psych development

8. Patient Care and Nutrition

Nutrition and calorie replacing is necessary due to chronic diarrhea, which significantly affects the outcome of trials

Pain management protocol is needed, and long-term follow-up for infants who received anti-retroviral therapies in trials such as 076 to determine "late effects".

At a meeting of the Patient Care Working Group:Pediatrics, a video was shown that is being used by Johns Hopkins to recruit women into 076. After it was shown, the issue of cultural sensitivity was raised, and someone said it should be dubbed into Spanish. Somebody else said that this was inadequate, and that it should be recast with Latinas.

Adolescents

There is no working group for adolescents. In the CCG meeting, Carol DiPaolo, the pediatric rep, said that early adolescents may require special attention because of the onset of puberty. In another meeting,

Diane Wara said that she didn't think a separate set of adolescent trials would be necessary. A recent article on adolescent epidemiology suggests otherwise:

Evidence from studies of HIV infection in people with hemophilia suggests that infected adolescents may have a lower rate of progression to AIDS or a longer incubation period and may tolerate severe immunodeficiency better than adults. More data from a wider range of patients are needed to better understand the natural history and to determine whether factors unique to adolescents, such as the hormonal changes accompanying puberty, influence the clinical course of infection and progression to AIDS. 1

Pediatric Full Committee

26 Pediatric ACTUs, 50 including NICHD sites. There should be 60 by the end of the year.

As of the previous ACTG, there were 1220 children in trials; now there are 1600, counting perinatal trials, but not counting mothers.

Pediatrics recompetes separately from adult ACTUs. Ped recomp will be in Sep. '93, for a 4-year cycle.

Consensus Workshop on Perinatal Transmission-Siena, Italy Jan. '92

- Significant progress, including improved tests and field evaluations
- Age of diagnosis reduced from 18mos. to 6mos.
- Need to apply early diagnostic tests carefully, because of limited experience and non-standardized tests
- Factors affecting HIV diagnosis sensitivity in infants include timing, age, HIV-Ig, vaccines, disease and immune status, and timing
- PCR and culture seem best for young children (see Appendix 2).

Maternal transmission-geographic differences

Kenya	50%	Zambia	39%
Congo	49	Haiti	25
Malani	42	USA	25
Zaire	39		

1 Gayle HD and D'Angelo LJ Epidemiology of acquired immunodeficiency syndrome and human immunodeficiency virus infection in adolescents. Pediatric Infectious Disease J 1991;10:322-8

-First-born from vaginal delivery more likely (50%) to be infected than first born by C-section (38%).

Maternal risk factors

disease status

decrease in CD4 and CD4/CD8 ratio

p24 antigen positive

lack of antibody to gp120 V3 loop (no definitive conclusion on this yet)

increased risk of breast milk transmission during maternal primary infection

Yvonne Bryson (UCLA) gave this presentation, and said that a manuscript of the Siena conference is in preparation. (310-825-5235 fax 310-206-4764)

Pediatric Symposium: Vaccines and Immunoprophylaxis

Steps in vaccine development

Isolation of agent

Elucidation of natural history and immune response

Identification of animal model

Humoral immune response

infection-blocking antibodies

most data is on envelope-specific neutralizing antibody

Neutralizing antibody

V3 loop-different in different strains and geographic areas

-controversial as to whether presence or absence causes maternal fetal transmission

HIV-1 Specific ADCC

-antibody-dependent cellular toxicity

-role in protection unknown

-diminishes in late stages of illness

Difficulties in vaccine development

- genomic diversity of viral isolates
- group vs type-specificity of the host immune response
- enhancing antibodies
- limitations of animal models
- seroconversion of vaccines

SIV model-macaque monkeys a good model for experimental vaccines, especially for pediatric AIDS.

Envelope seems to induce immune response

Protection from infection or disease? Protection from disease seems to be a more achievable goal.

Whole inactivated virus vaccines-very effective, although the mechanism of protection is unclear. Subunit protein vaccines-ineffective to date. Recombinant vaccinia viruses show promise, as does the pseudovirus approach.

In seropositive trial at Walter Reed (gp160-IIIb) 19 out of 30 subjects had increased B & T cell response. 6 injections worked better than 3.

It is still not clear which immune response needs to be stimulated to protect from infection.

Possible roles for antibody therapy-

Prophylaxis for accidental needle sticks
Prevention of maternal-fetal transmission
Therapy

Agents for immunoprophylaxis-

MABS "Humanized" murine monoclonal antibody
HMABS Human monoclonal antibody
HIVIG broad antibody activity
high neutralizing antibody titers
variation in patient pools?
protection of chimpanzees before, but not after virus challenge

Possible cocktail of monoclonal antibodies before the end of the year.

PROTOCOL NOTES

Perinatal

082-Phase 1 AZT during pregnancy and labor

2 more methadone patients needed

increased (though not toxic) levels of AZT with methadone

8 hrs after delivery, dose levels slightly higher with continuous infusion

146-rCD4-IgG in pregnant women and newborns

too early to tell if HIV has been transmitted-infants are now HIV-

rCD4-IgG shorter half-life than IgG;appears safe in children

half-life of rCD4-IgG is shorter in infants-why?

185-HIVIG+AZT v IVIG + AZT in pregnant women and newborns

HIVIG is from people under 400 CD4

will enroll 400 women, 200ea. arm, under 500 CD4

endpoint-HIV transmission verified by culture

nested studies will include PK of HIVIG,immunologic & virologic studies,

& testing for IgA antibodies using PCR

competing studies could be a problem-sites have to let protocol team

know about type and schedule of competing studies. For example, if

a child fails on this study, she will have had AZT, and so won't qualify

for 152, which requires no anti-retro therapy for 6 wks prior.

team will look at IVIG and HIVIG for possible antibody effect on CMV

problem with Abbott, the HIVIG supplier, supposedly over an NIH contract

requirement. Actually, Abbott does not intend to develop HIVIG commercially

and is probably stalling for that reason. Trial was supposed to start

April 1.

THIS SPACE RESERVED FOR ABBOTT'S COMMITMENT TO

SAVING LIVES-WHENEVER

Pediatric

051-AZT + IVIG v AZT + placebo in symptomatic children

262 accrued, 56 died

At the previous ACTG, the death toll was 47, and there was some anguished discussion about this. Stephen Spector, protocol chair, said that if the DSMB, which had recently reviewed the study, had wanted it stopped, they would have done so.

Data should be keyed in by August. Some sites (11 out of 24 that have accrued patients) have not been sending in their data (at the full comm. mtg, Spector showed a transparency with the Tardy 11 listed). One of these is Oakland Children's Hosp. Ann Petru said that they had a computer problem, so there is a data entry backlog. The problem has been resolved (there, at least) and they should be getting help with the backlog. Study will be unblinded when data is in.

144- ddi (50 mg/kg) v ddi (150 mg/kg) in children unresponsive or intolerant to AZT

a popular trial rapidly accruing patients 122 enrolled-target was 140 target will be increased to 300, with PK studies being done on the first 140. This is an increase, and it's because the data from 128 (high v low dose AZT) is not as good as hoped.

152-AZT + ddi v AZT v ddi in symptomatic children

target accrual 600; 164 enrolled as of Apr 1.

good racial demographics, and good data compliance

AZT good at lower dose

PK is a requirement because AZT + ddi have not been studied together before in children (i.e., FDA requirement)

concern expressed again about competing trials-if children fail 182, they won't qualify for this

170-Steroids for PCP in children under 2 yrs

"suspected" PCP sufficient, documented within 7 days of enrollment

blinded, placebo-controlled with primary endpoint at 120 hrs-after that, children will get open-label steroids

stratify by respiratory failure

as many as 30-40% of children die from 1st episode of PCP

in an adult study (in N.E. J of Med) people on steroids tolerated TMP/SMX better than those on placebo

170-continued

Diane Wara spoke vehemently against this trial. She said it was unethical, and that UCSF, and many other centers, will not participate. She said accrual could take 7-9 years. She instructed the researcher to look at accrual by the end of summer, and to decide whether to continue the trial. Ross McKinney (from Duke) said she was being unfair to the study. He was giving the presentation.

182-AZT v placebo in asymptomatic children under 9 mos.

will require a lot of clinical management

team decided to exclude serious bacterial infections, since that might mean that children are becoming symptomatic

will allow treatment with "another drug with no anti-retroviral activity"

there was concern that the protocol not be too restrictive with respect to concurrent medications

expected accrual-10 per month

the Protocol Team reviewed the 0.7 version. The revisions will go into the next (1.0) version, which should be available by the week ending May 15, per the Operations Office. This needs to be looked at carefully

Example of a protocol capsule

Pediatric C.I.
Working Group

Walter T. Hughes, M.D.
03/10/92

Prophylaxis for P. carinii Pneumonia (PCP) in Infants and Children with HIV Infection

A new anti-*P. carinii* drug, 566C80, is a hydroxynaphthoquinone with a high profile for safety. Efficacy for mild and moderately severe PCP has been demonstrated in adults with AIDS. Phase I studies have been completed in infants and children with HIV infection. Because of oral administration, remarkable safety, long half-life (50 hrs) and potent antiprophylactic activity in animal studies a clinical trial for prophylactic use in infants and children with HIV infection is warranted.

A proposed study would randomize infants and children to receive either trimethoprim-sulfamethoxazole (TMP-SMZ) or 566C80 in a double-blind study. Patients who qualify for prophylaxis by C.D.C. guidelines will qualify. Stratification will be determined by CD₄ T lymphocyte counts and prior episodes of PCP. The primary endpoint for efficacy will be occurrence of PCP while on one of the drugs. Secondary analysis will include rate of adverse effects. The study should be powered to determine if 566C80 is less effective in preventing PCP than TMP-SMZ.

Appendix 1

from the Consensus Workshop Meeting-

"HIV Mother-to-Child Transmission: Maternal Risk Factors
and Early Diagnosis" Siena, Italy Jan. 16-19,1992.

COMPARISON OF DIAGNOSTOC METHODS by various criteria,on a scale of 1
to 4, with 4 being best

Method	Reliability Sensi- tivity	Speci- ficity	Technical Base	Time	Specimen Collection	Low Cost
Culture	3	4	1	1	2	1
PCR	4	3	3	4	2	1
P-24	2	3	4	4	4	4
IgA	2	2	4	4	4	3
IVAP	3	2*	3	1	2	3
ELISPOT	3	2*	2	3	2	3

*non-specificity in infants less than 2 mos. old, but may improve
with technical modifications

COMPARISON OF SENSITIVITY OF METHODS AT VARIOUS INFANT AGES in percentages

Method	1 Week	2-4 Weeks	1-2mos.	3-6mos.	+6mos.
Culture	30-50	50	70-90	+95	+95
PCR	30-50	50	70-90	+95	+95
P24	10-25	20-50	30-60	30-50	20-40
IgA	-10	10-30	20-50	50-80	70-90
IVAP	NA	NA	NA	+95	+95
ELISPOT	NA	NA	NA	+95	+95

ACTG PCR WORKSHOP Part 2.Sunday 4/12/92.

The first part of the second portion of the PCR workshop consisted of several presentations by companies involved in the development PCR tests.

Many companies are devoting efforts into RNA PCR tests. One benefit of an RNA PCR over DNA PCR is to evaluate disease progression correlated with viral burden. The thinking behind the RNA tests is based on the observation that during viral replication there will be a greater amount of RNA as opposed to inactivated or latent virus. However, PCR evaluates the number of DNA pairs therefor, RT(reverse transcriptase) is added to a selected region of RNA to form DNA. If HIV(1) were the type of virus that had double stranded RNA that would work as well, but currently this is a necessary step to display accurate quantitation of HIV DNA pairs.RNA that is free floating is also easily broken in the PCR process.There is also great effort by companies to use PCR test for other Viruses.

A.) Roche PCR Assay kit. DRAGON.

Dragon briefly discussed the Roche DNA PCR test used to determine the Inhibitory Concentration(IC50) of HIV to AZT in 27 pts.(patients).[Resistance] The 70mt (mutant type codon) to 215mt-219mt domain is the targeted region. Findings include a lower IC50# v/s other methods of evaluation (not mentioned specifically at this time). There are complications with the development of most existing PCR tests. In the Roche test there are specificity concerns as to whether measuring DNA indicates something different cytopathologically as opposed to the measurement of p24 RT production. Another area which raises a specificity question is if this process measures inhibition or is there no target. The roche test is NOT quantifiable; it is used in information gathering(UD# is not a quantification)

B.)Gen Probe Chemiluminescent DNA Probe Detection KIT. McDonough. This is an HIV(1) specific test. A chemiluminescent acrylidion (sp) ester added during the amplification step of the PCR process gives indication of DNA presence by very visible and reflective light units, in 2 seconds, with little loss over time. (How little is little, probably a very good question). An advantage of this process is that the probe is protected from hydrolysis during the PCR amplification process.Cost was not addressed.

C.)AN immune Capture assay for semi-quantification of plasma DNA. Henard. Abbot Labs.

Abbot uses a monoclonal antibody(ab,antibodies produced by a single cell or its identical progeny, specific to given antigen. a useful tool to identify specific protein molecules.)to the gp120 and gp140 protein to capture infected varions in serum and plasma. The process includes a step where Heparin (anticoagulant) and citrate are utilized and reports that there were no significant differences in results when using these compounds. Henard also stated that with 9 thaws no significant differences in results found.Abbot tested the process between labs(not stating which labs) and including the

2

variable that all labs have a different set of parameters used in PCR testing, similar results existed. The discriminatory comparability was one log.

D.) other assays. Div. of Virology in Middlesex Eng. Discussion of a study to evaluate AZT resistance. Dr. Samples lab used 1000ml plasma/serum, then washed w/ rt buffer, then wash w/ comparable detergents followed by Quant. PCR and pt. mutations to indicate AZT resistance. The signal, non radioactive probe, indicates DNA/RNA. Samples found RNA falls early with AZT. Samples found a high mutation viremia in plasma compared to proviral DNA. Samples claims the process used here could increase result at a lower cost. Someone questioned that this is semi quantitative opposed to quantitative. (?)

Chiron Nucleic Acid Probe, Branch (b) DNA. Another means to achieve an effective quantitative result uses bDNA, a wash, a chemiluminescent probe, and finally a substrate to obtain quantitative result. A very colorful graphic presentation. Chiron sent the test to various labs and received conflicting responses in comparing the bDNA assay to rt PCR; some labs show the rt PCR to be more reproducible, others the bDNA PCR. Frozen samples are used. One person indicated that time prior to freezing a sample may cause significant changes in result.

Immune Response Corp. Intra and Inter assay to evaluate Viral burden in HIV1 Disease w/ immunotherapy. Results of indicate 60% of test for both inter and intra assay has very strong reproducibility (38% had less strong signal)

D.) PCR in MACS Cohort Study. Wolinski.

This was a brief presentation which depicts sensitivity comparisons between different PCR tests by various companies and various ACTUs. 93% overall sensitivity b/w 3 labs with the Gen Probe assay, 5 x copies each. 100% sensitivity w Roche assay, 5 x copies, at 3x Roche sites and 5 ACTGUs.

the MACS study considers reproducibility issues.

.Is viral load measured by end pt. dilution or standard curve?

.Is the amplification with in a linear range following the establishment of the linear range?

.To test lower end sensitivity using the Poisson Distribution formula $\{1 - (ump(k))\}$, and how to account for multiple copies.

E.) Applications of commercial assays in ACTG studies. Jackson, vice chair Virology Core Comm., chair of PCR sub comm.

Goals of PCR sub comm.

1. Standardize quantitative and qualitative DNA RNA PCR assays.

2. Evaluate sensitivity, specificity, reproducibility of PCR assays in Virology labs used in ACTG studies.

3. Establish a quality assurance program for the ACTGs.

4. Incorporate a qualitative DNA PCR assay into ACTG pediatric protocols for new born infants.

5. Incorporate quantitative DNA PCR assay into ACTG protocols to depict correlations b/w viral DNA/RNA titers, disease stage and disease progression, and the correlations in response to antiviral treatment.

6. Standardize a PCR test for Viral resistance.

Jackson then discussed Gen Probe assay stating that it showed 100% sensitivity and specificity. The Roche, with contamination

problems, had 98% sensitivity.

Pediatrics. A PCR study to indicate HIV transmission shows 98% positive for mothers, 10/34 infants positive (so far, study incomplete), 5 deaths. Evaluations at 2 weeks(wks), 6 wks, and one year.

Differences between virological regional labs(VRL).

3 labs sent random blind samples for evaluation. Case West.(Oh.), Stanford(Ca), USC. USC had very different results on 2 samples. PCR is to be used in ACTG 175, 6x samples per entry. VRLs will also be used in 175 therefor, a quality assurance of each lab needs to be established to assure accuracy.

Does treatment decrease viral burden?

Jackson indicates a preference of a linear standard curve opposed to end point dilutions with isotopic qualitative probes for detection of virus to effectively evaluate resistance.

Dilution control.

To assure accuracy Jackson states to do one qualitative and one quantitative evaluation. Each assay has its own standard w/ lab variables. One lab compare results of all protocols. If there are great differences in more than one lab, how different in the same lab? RNA titer has 1 log variability. Variables to control; many state of the art PCRs don't hold well but consensus may be achieved with similar results/similar technologies. Use one lab?

Coombs Correlation of RNA PCR and Plasma Viremia in Pts. on ZDV.

The objective is to establish a correlation of disease progression using plasma viremia and RNA PCR w/ ZDV Rx. Results of studies show that there is a rise in RNA signal for first 12 wks., then a decline below baseline, then a stabilization.

DNA v/s RNA PCR in ACTG

-uncertain of standard specific preparation techniques/ approaches may focus on similar pt.

-Currently Phase 1/2 tests use DNA PCR to detect change in viral markers.

-Phase 2/3 tests may use PCR to show correlation with long term outcome.

-PCR currently being standardized.

Used to compare quantitative assays in culture systems.

4/12/92 Virology Technical Advisory Comm. Meeting

Chair J. Gold.M.D.,

Agenda

1) status of new and current Virology Labs.(VL)

2) Criteria for Quantitative Microculture Quality.

3) Status of PCR QA(quality assurance)

4) Resistance QA

1. STATUS> To approach an accurate/effective means to evaluate lab status within current budget allocations the Virology Technical Advisory Committee (VTAC) devised a formula and point system for accuracy and accreditation. First a letter was circulated to all site discussing cost containment and the need to centralize into core and reference labs associated w various clinics. There are 3 parts to RFA submittal: A, clinic, a must to receive c 1, and must have c 1 to obtain c 3. B, c 1 core Virology comp. C, c 3 Development Virology comp.

41

If a lab can't afford to complete c 1 testing in VCL (core labs), c3 is then used to supplement c 1. Provided steps A through C grant adequate funding in the first place. Once again we were reminded of the election year.

Currently 15 labs were awarded to do p24 w/ qualitative cell cultures. VTAC plans to add the p 24 antigen test back into the ACTG process. The second step is to conduct phase 1/2 testing at core labs only. Step 3 is to add quantitative microculture into phase 2/3 substudies limited to core labs only. Phase 1/2 plasma viremia /resistance studies to be shipped to a core facility.

Funding problems are compounded by the expanding ACTG system. All labs participate in the QA program. The QA program assesses accuracy by a formula which was explained in detail. Sites receive point deductions for missing or contaminated wells based on an established curve relative to all labs. A lab may lose up to 20 pts. (time frame not stated) to lose accreditation. As points are deducted there are means to fix problems and maintain the capacity to complete testing however the incentive system applies and recruitment becomes another factor.

2) Criteria for quantitative Macro/micro culture QA
Again the point system penalizes for Infected Units per Million, 20 pts for false positive based on established curve and -10 pts for false neg. Missing data - 3 pts., Missing assay -20 pts. This test is costly and complex. Establishing effective confidence intervals are crucial not only for accuracy but for certification of tests eg. PCR.

QA status now assured lab quality >5%.

Recompetition:

Provisional Certification 7 labs

Probational 12 labs

not evaluated 3 labs

not approved 2 labs

sites added 1992:

adult 8

Pediatric 9

Overall lab scoring

Performance rating	Score
--------------------	-------

Certified	1
-----------	---

Provisionally Certified	2
-------------------------	---

Probation	3
-----------	---

Voluntary Probation	4
---------------------	---

The Virology core comm. evaluates overall performance of a given technique by using the sum of the scores from the 4 most recent, consecutive testing intervals to determine the need for corrective or disciplinary action as follows:

score	overall rating	action
<7	approved	o
7-9	provisionally approved	o
10-13	not approved	Individually reviewed by core comm. and possible

suspension of performance of assay in question for a specified period of time

>13 Mandatory Expulsion

Must Discontinue assay in

question, maintain a patient sample storage and inventory for current and future protocols requiring the assay in question and make necessary arrangements to have the protocol mandated testing at a certified VL including financial compensation for the testing performed at the certified lab.

3) PCR QA

Brooks

QA for PCR will only evaluate 10 ACTG labs, 4MACs labs with some overlapping. No WITS labs.

Drug companies do not pay for ACTG studies with their PCR tests

Data presented from NWU: blind study

Gen Probe; 3/4 met criteria

Roche; 1/4 met criteria

A real time QA blind pellet assay every PCR run will give feedback on validity. Review quarterly, careful watch if 2x runs are invalid.

4) Resistance assay

Krumpacker

Whole culture PBMC based assay

Follow consensus protocol (approved by the Virology Reference Labs) current cost needs lowering from \$300 to \$100-108 by reducing viral stock titration from 6 to 3 days (\$60) and Viral susceptibility test assay to \$48 per assay by pooling results to calculate IC50. Technician time not included in cost.

Resistance assay used in the 116, 117, 118 for phenotypic susceptibility AZT/DDI.

4-13-92

8:00-10:00 Plenary attended (Reported by other members)

10:00 - 12:15

Neurology Core Comm.

A meeting was held at the previous ACTG to discuss the problems of the Neurological Comm with in the existing ACTG system and structure based on the observation that this comm. has never been able to run a successful trial. Among solutions to the problems addressed in this meeting was the addition of a Medical Officer to the Neuro Comm. Joe Timpone is the new Medical Officer.

A question which still kind of hangs there is the capacity to run successful trials. There continues to be a lack of interest by many sites to run Neuro. trials. On the other designing trials of little complexity will also help increase interest in Neuro trials. Nesting trials onto OI and Primary Infection trials is necessary. Currently there are four ACTGUs with strong support for Neurological studies: UCSF, Seattle Wa., U of Minnesota, Washington U in St. Louis. 9 ACTGUs have some support (not adequate), 15 ACTGUs have no support.

The Neuro Comm. circulated a letter to each site to assess support capabilities of each ACTU. A compounding factor to this deficit of support is the development of trials that are up to date with the current state of the art treatments (even better if the trials are prospective). The N Comm. has a history of playing catch up to the work of the other committees. To attempt to gain support the comm stresses enthusiasm in presenting the scientific questions to either committee. The N Comm. recognizes the need to be involved in the development of protocols of the Primary Infection Comm. & the

O.I. Comm. and working groups for all phases of testing. The Pr.Inf.Comm. has responded positively to requests to have Neuro Comm. representation in all the phase working groups as well as a member on the Pr.Inf.Comm. DR. Clifford will be a representative on the Pr.Inf.Core; Karl Kiebertz, phase 2-3 working group (WG), J. Timponi the Combination Therapy WG, J. McCarthur the phase 1-2 WG. Mark Mintz; Pediatric Neurology

The O.I. Comm. Did not respond to the request for representation. The N Comm. may be able to do small studies in supported ACTUs and recognizes that "incentive ACTG funding" and definite need for support from drug companies, grants other gov./NIH institutions (NINDS, NIMH, NCI...) will insure possible adequate means to assure appropriate testing. The comm intends to create tests that are less complex to increase interest/incentive.

ACTGs #193, #175 are examples of the need for direct input into trial design.

CS:384 #175- ACTG 175 is a randomized, Double-blind Phase 2-3 trial of monotherapy vs Combination Therapy with Nucleoside Analogues in HIV infected persons with CD4 $\geq$ 200 and $\leq$ 500 cmm. Q.S. 384

Myopathy is a complication of HIV infection of underdocumented (undocumented) prevalence. Myopathy may occur at any time in disease progression with no correlation established with disease progression however, Myopathy may be associated with wasting syndrome. Myopathy is typified by muscle weakness. Myopathy is generally defined as a disease of muscular tissues (often meaning skeletal muscle). Myopathy is also a complication associated with ZDV Rx. Features of ZDV Rx associated Myopathy include muscle weakness, myalgia (muscle pain), elevated CPK (creatine phosphokinase; a catalyzing enzyme involved in the transfer of phosphocreatine to ADP to form creatine and ATP involved in muscle contraction), abnormal EMG, and abnormal muscle biopsy. Mitochondrial abnormalities on muscle biopsy are reported to be pathognomonic of ZDV Rx. When ZDV related myopathies develop symptoms may or may not subside when the Rx is withdrawn. DDI/DDC are not myotoxic but clearly damage peripheral nerves.

Originally the N Comm. intended to nest a series of non complicated non labor intensive studies into a larger macro study of neurological progression, a micro study to evaluate any need for further attention to the development of myopathies and to determine if the incidence of myopathy is greater with ZDV rx. A short questionnaire (10 Minutes) for the participant to fill out, and CPK serum evaluation (which could be scheduled w/ other lab work). If there is suggestion of myopathy a referral would be made to an ACTG Neurologist.

Sounds good. Important. But, by playing catch up there would be no effective means to include this study in the #175 protocol. This stimulated a lengthy discussion prior to a throwing up of hands,

Frustrating.....

A peripheral neuropathy study ^{questionnaire} ~~assessment~~ is part of #175. The comm. developed a generic form which is non labor intensive. If per. Neuropathy begins to develop a tool named a vibatron (\$2000) will detect shifting in per. nerves from baseline and is becoming an important assessment tool. Not all sites have them. This is also

7

to be used in #193. *# questionnaire may not be as reliable as skilled ~~evaluations~~ evaluations.*
Dementia...

ACTG #162 is up and running w/ 0 /36 targeted enrollment. The study is a Randomized, Double Blinded, Placebo-controlled trial of Nimodipine for Neurological Manifestations of HIV1 concurrent w ZDV Rx. Nimodipine is a Calcium Channel Blocking agent used primarily for hemorrhages. The thinking behind the use of Calcium Channel Blocking Agents for Aids Dementia Complex is from observation of elevated Calcium levels in the CSF (Cerebral Spinal Fluid, removed routinely by spinal tap) and the NMDA receptor correlation with cognitive impairments. There are currently 3 sites registered to run this trial (UCSF included). There is a question as to how long post study Miles Davies will supply post study drug the committee requests up to one year (at least) open label post study completion. The comm. would also like the drug co. to cover neuropsych testing. The comm. intends to give the Primary Investigators credits for taking on Neurological studies as an incentive for possible interest. Even with the incidence of ADC there are Neurological studies receive no financial incentive.

This lead to discussion of #193. ACTG #193 is a salvage protocol in development. Originally designed as a Randomized, Double Blind study comparing combination to alternating therapy w Nucleoside Analogues for Advanced HIV disease (cd4 < 50mm w history of prior nucleoside therapy). The N Comm. was involved in the development of this protocol. A Macro study for neurological progressing was to be written into this protocol. The population participating in this protocol are likely to develop any number of neurological complications including ADC (AIDS Dementia Complex), Peripheral Neuropathies, CMV related neurological complications.....

The Macro study would involve neuropsych testing and training of staff to effectively do the testing. IT would also involve peripheral Neuropathy testing as well. The Committee discussed means to answer the questions without such complication.

The progress was set back in the early development of the protocol where in the original Neuro progression study was left out (with out answer as to why, how, who). This caused the n comm to have to present concept sheets to nest the study into the protocol. Incidentally at this time the protocol has also been changed to include prophylaxis and to not be double blind (that's a lot of pills a day no matter what happens 32+)

The N Comm decided not to continue efforts to add the Macro study onto #175 because the incidence of ADC is prospected to be too low to be significant.

The N Comm discussed briefly a potential trial for Nerve Growth Factor (NGF) for peripheral Neuropathy. NGF is a newly discovered growth factor/protein which controls the development of sympathetic postganglionic neurons and ~~potentially~~ sensory (dorsal root) ganglion cells. Early animal studies show that NGF ~~may~~ regenerate and potentially protect peripheral nerves. NGF is too large of a protein to cross the BBB (blood / brain barrier). Genentech is currently directing tests with NGF and chemotherapy agents (Cisplatin {sp} / Taxol). Animal studies are underway but there is no current information on safety/efficacy in animals. Dr. Clifford

8

stated that he thought it will be one or two years before reaching the ACTG system. There is currently no known concept sheet for NGF.

PML: progressive Multifocal leukoencephalopathy: PML is a demyelinating disease characterized by progressive white matter lesions of the brain caused by the reactivation of the J.C. (Jacob Creutzfeldt) papovavirus. The J.C. virus infects oligodendrocyte which are the type of brain cell responsible for the production of myelin. Myelin protects nerves. Without protection nerves die and brain lesions form. Prognosis is poor and fatality very likely, though there are a few documented cases of 'recovery'. PML affects about 4% of people w/ AIDS (1987) the same researcher has stated that the rate may be as high as 10% (1991). Most people have antibodies for JC by age 5 therefore detecting JC in the peripheral blood is ~~not~~^{not} an effective means for diagnosis. Dr. McGuire (UCSF) is currently working on a CSF test for active JC Virus. PML diagnosis includes a number of symptoms; generalized and or localized weakness of one side of the body or limbs, blurred or loss of vision (possibly on one side), cognitive impairments ranging from language impairment to confusion, disorientation, or a loss of balance. Lesions are detected by CT or MRI scanning. Final diagnosis by brain biopsy. Toxoplasmosis, ADC, Cryptococcal meningitis, CNS related CMV must be ruled out. Currently there is no potentially effective treatments complicated by the lack of an animal model to test possible treatments.

The Neuro Comm. discussed a need for a trial and intends to develop a concept sheet for cytosine arabinoside (ARA-C) for PML. Studies presented at last years Int. AIDS Conference {VOL.1:191}{mb2037} treated pts w/ 2mg/kg iv in 5 day cycles. Neurological improvements followed the 3 courses of treatment w/ partial lesion resolution (by MRI scan). Symptoms did not completely resolve in any pts. Another route to administer ara-C is via intrathecal shunt. This may be effective but an early diagnosis will be the key to survival. Another option may be a comparison bw ara C and aInf. (alpha Interferon).

CS 346 CMV polyradiculopathy {polyradiculomyelopathy: presents acute lower extremity paresis / sphincter dysfunction/ life expect 8 wks post diagnosis}. Ganciclovir 5 mg/kg intravenous q every 12 hours 14 days. 6 mg/kg/q every other day, 10 doses. Then ~~500~~⁵⁰⁰ mg/kg bi weekly for 8 doses. Antiviral Rx treated as in other Ganciclovir trials. This cs continues to move along the protocol development process and has passed the OI Comm, The other viruses WG, The exec. Comm, and is in current development into protocol draft.

THE NEURO COMM SUMMARY:

The committee seems to be motivated and realizing their limited capacity. The comm. needs to continue to assert themselves to make the developing representation onto other committees meaningful and effective. The comm. Recognizes that other means than the ACTG are necessary to answer many of the scientific questions. The comm. must pursue active communication with the Prim. Infect. Comm. and OI

Comm. Leadership and enthusiasm are helpful qualities to make this an effective effort.

Activist may target the Prim.Inf.Comm. and will again attempt to meet with the NINDS,NIMH to do Neuro Trials.

11

12:15-1:15 actg 162

See previous report.

1:00-3:00 Virology Protocol Virologists
Chair S. Rasheed.

This comm is suddenly expanded with the recompetition form 15-20 previous site to up to 60.

The program office is to circulate a list of Virologist.

The Protocol Virologist are a sub comm. of the Virology Comm.

The protocol virologist either ask to be involved in protocol development or find themselves assigned to a protocol team. At this particular meeting there were many new members and the sub comm. needed to figure out how to accommodate with the expansion.

The sub comm. asked individuals to state their preferred area of interest. The response was slow.

The goals of the comm. discussed were to increase proper virology in trials, to find virologist for developing protocols and to evaluate completed protocol virology on stored samples.

To increase proper virology this comm. is involved in sample tracking for QA purposes. The information is then bounced to the data resource wg. It is the responsibility of this comm to also advise protocol team which lab information will be relevant.

For example end points bases on virological tests (PCR), or p24 testing. All factors such as storage, freezing, increases in the number of samples, centralized labs were mentioned but not discussed in great detail to report. like most committees, there is little financial incentive for efforts and a need to find creative support is often a necessity.

The comm. attempted to obtain volunteers for protocols 193, and three OI trials. There were no final commitments discussed in this meeting.

3:15-4:15 V.Comm. Tech Advisory Comm. Members only..... It was suggested that I leave as well as other members of other V. comm.'s.

I did so.

4:30- 5:30 V. Comm Resistance WG

Chairs C. Crumpacker, R. D'Aquila

One of the main objectives of the Virology comm.(VC), is to develop accurate measurements of HIV viral load in peripheral blood to monitor disease progression, responde to Tx (Treatments) and the significance of resistance. The VCRWG (Virology Comm. Resistance Working Group) has developed a consensus protocol to be used in all approved VL's (Virology Labs) to assess HIV Drug Susceptibility (for ZDV)(current version 1.2, replaces all other versions).

(copies available upon request). The VCRWG has submitted two concept sheets (NWCS 025, NWCS 024A, ACTG #152 ZDV alone v/s DDI alone v/s ZDV+DDI in symptomatic HIV+ children, Coordination of 016 serostudy w reference to NWCS 024 respectively.) Both cs's have passed the executive committee for protocol development.

Resistance is evaluated by a process called end point dilution and by Pt mutation. This process involves utilizing a 24 well tray and isolating proviral pairs, then adding the drug, and evaluating the Viral DNA pairs to locate the regions resistant. HIV has a variety of regions of mutation (41 mat leu, 70, 215, 219, 67 regions resistant to ZDV). Two common methods to locate HIV resistant strains are genotyping and phenotyping (genotype is the genetic information, phenotype is the physical properties of an organism determined by genotype and environment).

The VC would like to design studies that include resistance as a factor. Evaluations of how resistance relates to clinical significance related to Dz (Disease) progression are a priority for the VC (#143 analyzed). The development of a consensus protocol involved an evaluation of inter lab variation (TCID 50) to determine the QA/QC of the available methods for resistance. AN inter/intralab evaluation needs to be completed. Data of the inter lab evaluation to determine a TCID 50 by determining <.05 log between upper and lower trays. Results for 2 labs shown and there was adequate consistency. Results of a study of pooling wells comparing p24/IC50 resistance with AZT and DDI showed no differences of significance for sensitivity or IC50 for either AZT/DDI. p24 with DDI showed a > variation in the non pooled. p24 with AZT showed a slight > variation with non pooled v/s pooled. A third comparison of p24 end point vs rt based endpoint showed inconclusive data ; IC50 rt .088 / IC50 HIVag.118. Pooling may reduce costs from \$200 to \$100 a kit. Standardization of inoculation and culture conditions are established as well. This is important because the IC50 determination may be effected by various culture and inoculation conditions.

nwcs025 ACTG 152

This is a nested study to determine a correlation between PK and resistance. Secondly to determine sensitivity to antiretroviral Tx. and Dz progression. Third to determine the rate of development compared to dz progression. 36 sites to store isolates. Standardization method correlated with pharmacokinetics. Cost \$50,000.00 / 600 target.

Resistance with TAT gene Inhibitor.
Richmond UCSD...

A. NO significant data @ resistance discussed.

Invitro 20 wks AZT/TAT cultured with different isolates, no change in phenotype in terms of susceptibility. richmond reported that in vitro 6/7 cell lines worked; MT4 did not work due to protein changes. PBMC, macrophage it works....

6:00-7:00 #193 investigators meeting
see neurology report.

7:00- 9:30

Community Advisory Board Network Meeting

1.) open discussion for complaints (mostly) and problematic areas. There are many new CAB's and the idea of an orientation at the next

ACTG was suggested Harvard CAB members(?) offered to do this. There still needs to be some clarification in the roles of CCG and CAB reps.

A very important aspect of discussion was CAB networking of which each individual is responsible to uphold their efforts to the committees and CCG reps. Again, sign up sheets were circulated. Linda Dee stated that previous circulated efforts to CABS had poor response. If a CAB rep has difficulty obtaining materials or receiving calls from CCG rep of which they may be attempted to reach, they may contact K.Fong or L.Dee.

Concept sheets are only available after they are approved by the Executive Comm. and through each site.

Cornell CAB developed a survey previously circulated to all CAB's for approval (UCSF approved with modifications). The survey is for accrual purposes.

The issue of translation was discussed. The UCSF CAB has translated ACTG 175 into Spanish. The PETT project has not pushed for translations leaving translations up to individual sites as a chore.

The Accrual Subcomm. presented a site comparison for accrual. I did not attend this nor the presentation on Pediatric CAB's. At this point I left to go to #188 meeting.....

#188 Neurodevelopmental and Neurological Study of HIV1+ infants and children in Clinical Trials.

#188 depends on accrual into 152 mostly. There are serious accrual problems in 152 which hold up progression of #188.

The Neurological testing takes 2 non consecutive days. Social workers are a great help in conducting the exams. Compliance is good, \$80. One hospital reports to have \$64 Latin recruitment, 35% overall Latin. One problem is that parents do not see how the Neuropsychological testing benefits the child. Neuropsychological exams help determine dz progression because development is very observable and generally predictable; a commonly used means of diagnosis for many diseases in children. The NIMH has developed a Neuropsychological exam in Spanish and is currently developing an exam that may not be biased due to learning disabilities, socio-economic factors or second language barriers (culturally sensitive) 4 14 92 Plenary Session attended at 8:30-10-00.

reported by other members.

12:30-2:30 Neurology Full Comm. See Previous NC report same information.

4:00-5:00 OI Systemic Mycoses Pathogen Study Group.....

059 Multicenter study comparison of Fluconazole and Amphotericin B as TX for Acute Cryptococcal Meningitis (CM). Pfizer co. completed under IND. More deaths occurred early in the Fluconazole arm than in the Ampho B arm. Arms= Ampho B 2mg/kg vs Fluconazole 200 or 400mg/kg. Fluconazole in IV form is approved however Ampho B is often used first especially if the case is severe. Flucytosine may be used with Ampho B in severe cases followed by Fluconazole.

ACTG 159 is a randomized double blind protocol comparing Ampho B with Flucytosine to Ampho B alone followed by a comparison of fluconazole and intraconazole in tx of acute cm in AIDS pts. This is a safety and efficacy study, phase 3. Stage 1: patients are stratified by mental status to either Ampho B .7 mg/kg IV x14 days+ Flucytosine 25mg/kg po q6h x 14 days OR Ampho B + placebo. Stage 2: Stratify by initial tx and by mental status at baseline then Randomize to either Fluconazole 400mg PO q12h x 2 days followed by 400mg PO qd. x 8 weeks+ intraconazole placebo OR Intraconazole 200 mg bid x 8 wks + Fluconazole placebo. Exclusion criteria includes high pressures w negative LP (lumbar puncture to sample CSF) and use of the anticonvulsant, Dilantin. (Valporic Acid ok for seizure complications) Rifampin and Dilantin OK at day 0 only. Warfarin, rifampin, oral contraceptives, hydrochlorothiazide, tagamet, sulfonylureas should be avoided w use of Fluconazole. Diagnostic procedures for CM include CRAG (cryptococcal antigen) in blood and CSF. Lumbar punctures (LPs) evaluated at baseline, weeks 4&10 and at the end. Subjects must complete previous studies to enter. At 10 weeks 3 CM cultures negative. 3/14 deaths at weeks 11&12. 4 dropouts w some seizures reported. 32 randomized into stage 2. Mild nausea reports.

#120 Pilot study to determine feasibility of intraconazole for Primary TX and suppression of relapse of disseminated Histoplasmosis in AIDS pts. Study closed w 62 pts 7/91. All pts off tx. (induction). 36 on tx, 8 off, 17 off study. Median duration 37.4 wks. Evaluation of data is slowed by missing induction data 1 pt missing ^{dispersion} of protocol tx, 2 pts missing baseline Hematology, 2 missing Histo targeted exams(?) intraconazole may be reformulated.

174 Pilot study to determine the feasibility of fluconazole for induction tx and suppression + relapse of disseminated Histoplasmosis in AIDS pts. Possibility of study drug by using time to resolution of symptoms, signs, reentogenographic and lab manifestations, also survival. Schema; severity of histo evaluation. IF histo is severe pts receive up to 250 mg Ampho B for up to 7 days prior to evaluation and/or enrollment. If Histo is severe at re-evaluation, the pt is not enrolled. Induction: day 1: Fluconazole 600 mg bid loading dose. (continued on next page)

14

day 2-56: Fluconazole 600mg qd maintenance, wks 9-60: Fluconazole 200 mg qd.

19/40 accrued. 3 discontinued due to toxicity (1st wk one, 4th and 8th wks other 2, one with skin lesions), 17 still on tx. 14/17 clinical response at end of 8wks, relapse 12/16 pts. MSG sites slow accrual. Response rate lower than expected may increase induction to 800mg and from 200mg to 400mg for maintenance. susceptibility data done on isolates in relapse pts. (data flashed and I missed it). Absorption questions, is absorption poor?

#202 IN development: Dexamethasone in CM.

placebo controlled double blind randomized safety and efficacy study

Dexamethasone 10mg IV loading dose; then 4mg q6h for 72h or placebo IV q6h. There is a question as to whether or not Fluconazole may be used instead of Placebo. Intercranial pressures evaluated. corticosteroids may decrease intercranial pressure and may be used at day 1 (1mg). CSF pressures and Nernst deficits evaluated at days: 1, 2, 3, 7, 14, weeks; 6, 10. Regionally directed to 4 sites.

981: Randomized Comparative Study of Fluconazole vs Clotrimazole Troches in prevention of serious fungal infection in advanced HIV/or AIDS pts. Phase 3. Efficacy, safety, tolerance, and survival in advanced HIV (t4 < 200 + participating in 081) treated w oral Fluconazole or clotrimazole troches for prophylaxis of serious fungal infections. 421/500 accrued. DSMB evaluated trial in 11-91, study to be analyzed w 081 data. 6 month to 1 year extension.

203: A phase 3 study of the safety and efficacy of combo alpha interferon (INF-a) and ZDV (AZT) (or other nucleoside analogues) in pts w/ HIV and Chronic Hepatitis C infection. In development. Toxicity of combo (stated above) is a concern, (neutropenia). Liver biopsy for Hep C, A non invasive marker would be nice. Dosing; aINF, 3 million units 3 x a week + nucleoside vs nucleoside alone. At 18 wks increase to 18 mil 3 x a week. If clinical progression patient will roll into aINF arm, no control arm. End points: normal ALT. PCR in serum for HCV.

204 Randomized double blind trial of BW256U87 prophylaxis for opportunistic Cytomegalovirus Dz in HIV +, CD4 < 100. BW256 is an acyclovir prodrug. The results of an English study will determine the dosage BW256 may increase to 3.2 gm per day vs acyclovir at Herpes dosage.

#169 Evaluation of SQ 32,756 (BV-ara-U) vs acyclovir in tx of localized Zoster in HIV+ pts. BM Squibb. Problem of detection of rashes in 72h, need to find the rash early for significant effect. Oral BV ara U vs acyclovir 5x a day. 79/159 pts accrued.

Wed. 4-15-92: Virology Core Comm :

Chair R. Coombs.

Review of the branching tree diagram for the VC (Virology Comm)

Other Viruses: S. Spector, PCR, JB Jackson, Resistance, C crumpacker & R D'Aquila, Pediatric Virology, J Sullivan, TVAC J. Gold. Protocol

Virologist, S Rasheed, Virology Labs, K Huberman, Quantitative, S Hammer.

This ACTG is deemed the coming out of the VC. I think this is due to the possible large scale use of PCR and the coming changes in centralization of research labs. Discussed previously in the VTAC report.

PCR tests have many variables to consider in each lab and from lab to lab. Assuring quality is an involved task and the reliability of the PCR is still in question because of the many variables to consider. There was never a mention of "the coming out of the VC" in any of the meetings I attended.

V lab goals reviewed:

- 1 develop virologic lab surrogate markers for clinical outcome. Develop measurements of Viral Load (VL) to monitor DZ progression. Develop measurements for a correlation bw VL and drug resistance e.g. 164/168. Conduction of real time testing for rapid assessment and turnaround.
- 2 Progress in area of quantifying cell free p24 in acid wash test. Evaluate DNA/RNA PCR tests and correlate w viral /immunological markers.
- 3 Study virus in CANS and reproductive systems.
- 4 Develop means to determine status of infant population.
- 5 development + implementation sensitivity assay of PBMC for resistance . 6 Prepare agenda for vaccine, immunotherapy, earlier intervention, chemotherapeutic studies.
- 8 Viral co pathogen study group to study other viruses; CMV, HPV, HCV, HBV, PML(?),
- 9 Virological assessment program to expand for inclusion in international trials.
- 10 Develop close collaboration w other agencies that conduct studies (NIH, NCI, ...) to continue to develop "tools of the trade"
- 11 Incorporate consensus protocols into ACTG studies for example: Conduct QA performance for cell dilution cultures, resistance studies, p24 antigen tests, evaluation of Elisa tests (164&168), evaluation of frozen samples (068 and 047 samples).
- Short term evaluation of real time samples.
- Quantified microculture/acid associated antigen in phase 1/2 testing. Relation of VL to resistance. PCR with VL.
- 12 develop concept sheets (cs) for virological generated protocols.

#175 Statement @ Plasma Viremia studies to be conducted in #175 were cost ineffective because of a predicted only 25% detection in this population. Power of test is low.

IN #175 there will be quantitative PCR tests done on each individual

6 times per year. The cost will be extreme, roughly 200-400 per test. This is exemplary of the power of certain committees to nest testing over others. This use of PCR tests is to validate the test. In my opinionated opinion this could be effectively done in a much smaller scale given the amount of factors that affect the test in

16

one given site.175 does not test of r reproducibility of the PCR test between labs.175 tests for correlation w dz progression with tx and viral burden.

#143 discussed : #143 is a study of combination Tx in asymptomatic pts. (Combo AZT & DDI). Cell dilution cultures are evaluated at baseline,12,and 24 weeks. There has been a 2 log decrease form baseline in cell dilution cultures with titers decreasing from 85% to 65% positive at 12 wks.

#168 & #164 data on the resistance of BIRG 587 w AZT. Observations of dramatic early drug effect in plasma cultures. An important question raised concerning the definition of a significant drop. A validation needs to be made if a 25 fold (2 dilution) vs 1 dilution variability is significant. The question hangs.

182 To diagnose infants ASAP using HIV1 PCR at VRL (Virology reference lab) NWU. QA for the PCR using real time new titer assay.False positive have been problematic in the past in this population. Uracil and glycolace may be in tubes to cause false result. There are inexpensive compounds available to clear tubes. The QA will involve a standardized qualitative and quantitative assay with evaluations for sensitivity, specificity,reproducibility.With the hope to establish a ACTG wide PCR program. Also to include the quantitative PCR into ACTG protocols,especially for entrance criteria for new borns.Another goal is to correlate DZ progression and responses to Tx with the DNA/RNA PCR titers.And as previously stated, to determine resistance to TX with PCR.Ped protocols will use dry blood spots to increase specimen volume.

Resistance was discussed in the Resistance working group report. Copathogen study group discussed its goal of predicting high risk for viral pathogens w HIV infection such as CMV, papaviruses,EBV,HepB/CV,and resistant Hep CV.Need to develop protocols and chairs or individuals interested form this committee and to work with the OI comm. Out of time.

Attended plenary + CCG meeting.

FOURTEENTH AIDS CLINICAL TRIALS GROUP MEETING

The Fourteenth ACTG Mtg. was my second and my impressions of the whole operation remained relatively the same even though I felt a little more prepared for this meeting. The general AIDS governmental bureaucracy still has huge problems but comparing the two meetings I've attended, I feel there is improvement in the way AIDS advocates and activists involved are gaining more recognition and respect. In several large meetings as well as small I saw researchers address the myriad of problems that the CCG and ACT UP has brought up. In one meeting on ACTG 207, Dr. Douglas Dieterich had a slide prepared to answer some of ACT UP Boston's concerns in that trial. Dr. Judith Feinberg actually asked ACT UP members to give their input in the new CMV PX trial (ACTG 204). I feel there is still improvements to be made, but it's good to know that all our hard work is gaining respect.

If there is any one problem I feel needs priority I feel it is the funding situation within the NIH, specifically at the ACTG. New research in all cmte.s seems to be at least slowed because of lack of future funding due to the federal cutbacks. I felt a sense of frustration with many scientists and doctors who cannot continue unless funding is increased. Additionally, TB, seems to have no priority in funding even though research is desperately needed in this area.

I'm going to report on tuberculosis and as many OI's as I can in this report.

TB Working Group

It was with surprise that many activists discovered upon arrival at the ACTG Mtg. that there was a meeting of the TB Wkg. Grp., let alone one even formed. Many New York physicians and activists are very frustrated at the TB problem and it was a bit of a relief to see that the ACTG was going to address the crisis in terms of research. However, going to the meeting it seemed that there are still many problems that need to be worked out with clinical trials in control, compliance, many scientific issues, as well as the general social concerns associated with TB. Additionally, the new concept sheets presented (CS. 385, 389, and 390) seem to not hold much promise according to some of the people present. Some is already known about ophlaxacin and sparfloxacin in clinical TX for TB.

Dr. Joyce Korvick who is a NIAID medical officer presented a plan or objectives of the TB Wkg. Grp:

- 1)Optimum of PX strategies (ACTG 177)
- 2)Trials to test existing agents for effectiveness for MDR-TB, (multi-drug resistant)
- 3)Trials to test combining of new agents for effectiveness for both TB and MDR-TB
- 4)Strategies for optimal TX practices; a)shorter course therapy, b)DOT (direct observance therapy), c)novel delivery systems, d)adjuvant therapies
- 5)Facilitate Phase I of new agents in order to speed their further clinical development in larger trials (this wasn't needed in the past, but is now.
- 6)Descriptive studies, a)survey of susceptibility, b)retrospective study of TX outcomes of MDR-TB, c)case control study for risk of developing active TB in patients w/ history of PX,

page two...

d)rate of infection in HCW by serial PPD testing, e)evaluate event rates in the homeless.

The ACTG is mostly interested in 1-5 of the objectives.

I also feel that studies need to be done in reoccurrence rates in HIV+ individuals, reliability of current TX regimens in HIV+ people, and studies of false negative skin tests and clear radiographs in HIV positives.

There was also a revelation of the TB Action Plan:

a)CPCRA for large Phase III trials, b)ACTG for PX trials, c)CDC for both Phase III and PX trials, and as trials get larger; d)a reference lab (sensitivity tests), e)clinical mgmt. (DOT), f)DAITRI (acceleration of Phase I drugs, fast track) g)DTB new drug development for PX and TX.

After this impressive plan was revealed Dr. Korvick said that Fauci asked what the TB Wkg. Grp. could do w/ existing funds and labs.

It's interesting to note that there was no other mention of how this plan was to be funded.

There is supposedly going to be some "shifting" of funds. The discussion then turned to ACTG 177, which also fits into the TB plan as optimum PX strategies. Dick Chaisson led this discussion. The trial is an open label two year accrual of INH for one year vs. Rifampin/Pyrazinamide for two months. The trial has had poor accrual w/ 100 patients enrolled and a target of 2000. Chaisson said that it was slow to accrue because of recompetition, however it is the thought of activists that people who test PPD+ will go ahead and take at least INH. it's thought that it works for PX. Adding CPCRA sites and the CDC may help accrual but there is a long way to go. There was also some thought as to what to do with the people w/ MDR who enter this trial not realizing that it won't help them at all. Of course this is why faster testing procedures need to be speeded up. There was later mention of this trial at other mtgs., however the team mtg. was cancelled later in the week. Linda Dee seemed to think trial might be scrapped because of it's accrual problems. There was further discussion of the concept sheets. the first is a salvage protocol for MDR-TB, single arm, ofloxacin plus two other antimycobacterial drugs. The trial is designed to evaluate this particular quinalone in MDR. Chaisson said that the drug is available and more studies have been done on it. One researcher had experience w/ ofloxacin in MDR and seems to think it doesn't work, that in fact nothing works. (People w/ AIDS and MDR just don't survive) Chaisson defended the trial saying that it may not be the best but it is available and the trial is of short duration. There was discussion of enrollment difficulty because of indentifying MDR and early death of patients w/ MDR. Also, there is concern that there should be a pediatric arm since so many children are becoming exposed to TB. There was concern about little known effects of quinalones in children. One more thing... sparfloxacin seems to be a more effective drug from the little research and experience w/ it, however ofloxacin is more bioavailable. (Many of these concerns may be moot since late breaking news shows that the Executive Cmte. is pushing forward w/ this trial and C.S.389) This trial is a single arm, open label w/ possible MDR patients, although not required because of difficulty

page three...

identifying MDR. the drug of choice here is sparflouxacin, pyrazinamide and ethambutol. Several points came up in the discussion of this trial. There seemed to be a definition problem in what denotes pulmonary and extra-pulmonary in terms of criteria, and what is disseminated TB; how sick is dis. TB? Comparative study for relapses needs to be done as well as a possible arm for HIV- persons which would aid in accrual. (The reason that INH and Rifampin are excluded is because of inclusion of MDR patients who most often are resistant to these two drugs.) The last trial is C.S. 390 which already seems to be dead so I'll just say a bit about it. It is a three arm comparative trial of three directly observed intermittent regimens for initial TX in pulmonary HIV+ people. Basically it seems that their was some power trips against the designers of this trial, however accrual was to be quite large making the study inefficient. Also the trial called for the use of kanamycin, an injectable, and several of the questions raised about all these trials also come up w/ this one. Those overall questions are that a lot more research needs to be done in the epidemiology of HIV and TB, new basic science on promising drugs, and the frightening problems of MDR and the fact that it's difficult to study because patients di so quickly.

There was some talk about the use of macrolides in TB and appears that they just don't work. (clarythromycin) Also discussed was the use of standard therapy in new ~~scenarios~~, that it is not good science in terms of finding out what drug works. SO... the news in TB research at the ACTG is quinalones, which are being used in some clinics, have limited efficacy, and generally seem unexciting.

There was an ad hoc mtg. of several of he NY doctors who are very worried and frustrated w/ the TB situation. Iris Long (from ACT UP/NY) and myself sat in on this mtg. The docs were obviously concerned about doing research at all because of the plethora of problems that exist w/ TB. Some of those problems are: Faster methods of identifying cultures, rapidity of smear negativity after TX, CDC not interested in doing comparative studies, difficult to do new protocols against standard therapy, finding out how infectious people are is hard to determine, accrual problems w/ his population, and last but not least...funding. It seems to me that the ACTG is not interested in TB because it is unglamorous and is so infectious. and contagious.

The single agent TX and PX of MAI was the next plenary I covered: Dr. Carol Kemper from Stanford and the California Collaborative TX Group presented three different regimens of the single agents of Ethambutol/Rifampin/Clofazimine/Ciprofloxacin. The study was for four wks. in patients w/ AIDS and MAI. Almost all clinical symptoms improved in the patients, some intolerance to at least one of the agents, and at least half had to discontinue due to toxicity. Another trial for more patients (60) w/ no prior TX was initiated to get more data. The Rif. and Clof. were not that impressive, however the ethambutol affected culture cts. Three patients became negative. The clinical symptoms seemed not to improve in this trial, patients kept losing weight and had gastrointestinal side effects. There was some thought that the at least ethamb. should be considered. Stanford is doing sen-

page four...

sitivity tests on samples and patients will be rolled over into combination therapy.

Lowell Young presented the next section on Azithromycin and Sparfloxacin. Azith. looks good in this data presented. It has a half life of 70-80 hours; the dosage being 500mgs a day. Patients were put on a maintenance dose after thirty days to 200mg a day. Virtually all patients had less fever, night sweats, however there was no change in weight. There was some toxicity in abdominal pains and diarrhea but no one discontinued the study. Azith. as a single agent reduces bacteremia, there is a clinical benefit after thirty days. It is safe, well tolerated. Resistance studies are being done.

The other data on Sparfloxacin did not look as good clinically, although the drug reduces bacteremia. (There was no data on how patients felt) There is no data on absorption; studies are planned. There was some dose limiting toxicities in CNS and photosensitivity. There was an addition of ethambutol after after three weeks. There seemed to be justification in additional cautious studies.

Dick Chaisson presented the next data on ACTG 157. It's a phase II, double blind, dose ranging (500-2000mg bid) no placebo study of clarithromycin in a twelve week study. There was 72 patients, some rolled over from Phase I. It will continue to 108 patients. This was an interim analysis. All isolates were susceptible to clar., there was some resistance. The most common adverse reactions were gastrointestinal upset. There was a significant improvement in symptoms. The resistance problem was met with patients being put on combo therapy after 12 wks. Overall it shows that the drug is very active against MAI, there was a significant dose response and clinical response showed equal responsiveness. Now it seems to me that anyone w/ MAI should be put on combo therapy similar to MAI-TB. (Combo of clarithromycin/ethambutol and azithromycin)

Stephen Nightengale presented the study of Rifabutin in PX for people w/ less than 200 cd4. It was two studies a) 580 patients completed in 1991, b) another trial of 556 patients. The result of this study is that patients who developed MAI were half as high from the first day of the study to the end for those on drug. The rif. patients clearly had a longer life span. Adverse reactions were found in 59% on drug and 51% off. Both studies show that rif. delays bacteremia. There was no difference in susceptibility. Nightengale felt that if culture was positive to add clarithromycin. (other drugs: clofazimine, ethambutol, ciprofloxacin) Some thought in initiating amacacin(sp) then adding four drug combo. The enrollment of women in this trial was questioned, some feeling that it was not proportionate to the population. The next session was the mycobacteria study group. the first trial discussed was ACTG 135. It is a four drug regimen of Rif., cipro., etham., clof. then addition of amikacin. There will be an addition of a maintenance study of azith. There are 67 patients enrolled, will increase to 90. Eight patients have finished the protocol with a median time of 21 weeks. The culture colony tests had dropped, there was fever reduction, less diarrhea in later study.

page five...

The update on ACTG 145 (penicillin G vs. ceftriaxone for neuro-syphilis.) The study has low enrollment; need to use existing MAC study. Probable reason for low enrollment is the exclusion of patients for prior antibiotic use in the past year. May reduce to past 6 months.

The ACTG 186 protocol for sinusitis PX is underway. The trial is a four arm double blind phase two study comparing the role of anti-inflammatory, antibacterial, and decongestant agents.

The PCP Pathogen Study Group was the next area I covered... PCP has become an OI that has had a lot of study and trials on and several completed studies have given us some very important answers in the control of the pathogen. New questions have arisen however and include: a) improve the toxicity of current drugs, (efficacy trade off between T/S and AP), b) need better drugs for active disease, better oral drugs, parenteral, adjunctive, more active agents.

In 081 an ongoing study will go to the DSMB by May. It will be extended to Jan. This would look at 3 anti-PCP agents w/AZT. The median t-cell is fifty; it will last two years. There was some question that this would turn into a one arm trial- but it appears to not be happening. The trial will recognize combo anti-retroviral therapy. Since there are less cases of PCP there is a problem accruing for large trials.

Sharon Safrin presented 108... Enrollment is poor even though the study has been open for a year. There are 99 patients @ 19 sites. It is to compare Dapsone/T/S vs. Clindamycin/Primaquine vs. T/S in TX of PCP. One regimen has been studied but not all have been approved. The study is designed to find out the best. Three problems have arisen in this trial: a) eligibility, some requirements may prevent patients from enrolling (intolerance to Septra), b) evaluability, patients lost to follow up, not using the standard cross over, c) enrollment, problem w/ access to PX, many patients are first time PCP, they have fallen through the cracks.

In ACTG 170 peds are having to take a placebo. They gave the reason that PCP is different than adult disease. There was concern again about enrollment because of less incidence of PCP in peds. The steroid issue was discussed, whether they are safe in this age group.

ACTG 173 was then discussed: The trial is open and running. It is a escalating multiple dose, Phase I, double blind, placebo controlled of the drug WR6206. The administrative and dosage problems have been worked out. (Originally the dosage was 60m per day but dropped to 30 escalating until tolerable. It was good to find out that there are similar drugs that will be available if this one is not successful. The main toxicities are hemoglobin and hematocrit deficiency.

The Protozoan Pathogen Study Group met and discussed updates from an English trial of letrozol and albendazole. The letrozol reduced diarrhea where the alben. stopped it and also cleared the symptoms. Stools were less frequent and more formed w/ this drug. Comparatively, the albendazole is the better drug according to this trial.

page six...

207 is a study of albendazole in TX for microsporidiosis. There was some weight gain reported as well as reduction of stool volume in 4 out of seven patients. Doesn't seem to be a fast acting drug. The dosage is 400mg bid. vs. placebo. Dr. Dieterich presented concerns from ACT UP/Boston as one of his slides. The concerns are that 28 days is too long for a placebo and that monthly biopsies are too much. Suggestions were given for drugs to be used in place of the placebo such as fluconazole and itraconazole. 198 is another trial of letrozole. In this trial the dosage is escalated from 10m to 100m. However no one has seen much results up to 100m. No one has tried that high dosage. Some feeling that there is not good enough absorption.

192 is a double blind, placebo, Phase I trial of paromomycin in crypto. in patients under 150cd4. There was early reports of decreased stool volume so far. The dose goes up to 3000mg a day. After 21 days if patient is on placebo, then they are crossed over to drug and escalate to 3000mg.

There was discussion that these drugs presented are only models for better drugs; that new drugs and trials need to be developed for crypto.

154 and the French study ANRS 003 were discussed next. The drug of choice is pyrimethamine in PX for toxo. The pyr. arm of this study looks quite toxic even though as TX the combo works. As PX there seems to be no would be no difference. The CPCRA study was closed because event rate was low. The comparative arm is aerosol pentamidine.

A Burroughs-Wellcome study of combo. of pyrimethamine and BW556C80 looks good in the animal model. 7 out of 8 patients enrolled showed radiographic improvement, but there was some relapse as well as erratic absorption. BW thinks that it may not be as good as standard therapy but could be good in combination.

Other Virus Working Group

This group met to discuss priorities in studies. CMV is to be at the top, w/ acyclovir resistant herpes second and Hepatitis II third. In terms of CMV lab issues are becoming more important than clinical, PX more important, and the resistance question. There was discussion of the need for more lab experts to develop better protocols, and a group to develop concepts for "other studies" that don't have groups. Again there was the problem of no money for development. This group seemed highly unorganized, however new and the meeting ended early.

System Mycoses Pathogen Study Group

ACTG 159 was discussed. The trial is double blind, randomized, enrolling 260 patients. The accrual is low at this time. Patients w/ first episode crypto. Everyone is given the amp B and the flucytosine, then after six weeks are randomized to either fluconazole or itraconazole. The interim data looks good, it's a safer study than previous ones. 70% became culture negative at two weeks. It seems to me that they may be having accrual problems because this trial is pretty much standard therapy. Dr. Joseph Wheat presented the data on ACTG 174 which is a pilot study to determine the feasibility of fluconazole for induction TX and suppression of relapse of Histoplasmosis. 17 patients had reached endpoint or been through the eight week induction.

6 were failures (5 non-responders 1 failure) The induction dose may be lowered and the maintenance may increase. Accrual for this trial is going well.

ACTG 202 was presented by Dr. Jeff Jacobsen. The study is a safety study, double blind, randomized, and w/ placebo of dexamethasone in cryptococcal meningitis. ACT UP had brought up concerns of using fluconazole instead of a placebo and the fact that there are so many spinal taps called for in this study. The researchers said that the taps are to keep people alive; that they relieve intracranial pressure, and that they simply need the info for the study. (Nevermind if they won't accrue because of this matter) There was some questions whether steroid use would effect adrenal glands, that they may not effect CSF.

There was a brief discussion of the use of fluconazole for PX of fungal infections and that resistant esophagitis hampered by this. There needs to be further studies. The prolonged immune-suppressed state increases fungus and not enough is known about

I'm not going to report on the ACTG 204 team mtg. because I was late to the mtg. I will say that it was a very positive, productive mtg. with ideas flowing freely between the researchers, SDAC, Burroughs people, and activists. The trial is of the BW pro-drug BW256 PX for CMV. Judy Fienburg had a lot of good questions to ask. An acyclovir arm was discussed and agreed to by most of the room. Some discussion of what markers to use because p24 antigen costs so much more. There was talk of the political differences in the PI cmte. and the OI cmte. in terms of more evaluations are done in PI.

The Wednesday Plenary was basically an overview of the entire conference but only included summary's from PI, OI, Women's, and Peds. The PI Cmte. is made up of 3 working groups: Phase I/II, Combo Therapy, and Phase II/III. In Phase I/II the studies are as follows: tat inhibitor (Roche), protease inhibitor (Roche), U-87201E (Upjohn), Soluble CD4-PE40 (Upjohn), Nevirapine (Birg), and the L-drugs which are closed.

Phase II/III trials are: 019, 155, 175, 193, and ddI trials-116/117/118.

The OI Cmte. is made up of: General Cmte., Core Cmte., 5 pathogen study groups, Multiple OI's, and PX. The goals are; 1) rapidly test OI's w/out current TX, 2) new therapies that are more effective but less toxic, and 3) validate unproven therapies. The five PSG's in the OI Cmte. are: MAI, CMV, Protozoan, PCP, Systemic Mycoses.

The Women's Cmte. has these subcmte.'s: gynecologic infection, epidemiology, protocol design, obstetrician/ped., at large.

Peds. discussed the integration of other ACTG studies to discover therapies applicable to all HIV infected. Find out why 90% of infants become infected by mothers at birth. Diagnosis needs to be studied.

Later in the day there was a CCG Mtg, which was an overview of the ACTG from community activist point of view.

page eight...

Members of the African American community attended the last CCG mtg. to push the ACTG in to studying Kemron, oral alpha-interferon. Their anecdotal evidence shows that the drug works, however the scientific data is not there. It was interesting to note that these people are coming to the ACTG like ACT UP did in order to get things changed. The CCG voted in favor to look into this, putting aside opinions whether the data was conclusive or not. Before I left DC I heard three reports from Mark Harrington, (PI), Michelle Roland (Oncology), Jesse Dobson (Immunology). Mark reported that the ddI data would probably push the FDA in to approval of ddC. He spoke of whether 193 (less than 50 cd4, double blind combo. or alt. therapy) should or shouldn't be blinded. D4T sustains t-cell increases better than AZT, however there appears to be more neuropathy than the other nucleosides. Other nucleosides to watch for are 3TC and FLT. The report on NAC is that it is not absorbed well at all levels; there seemed to be no change in glutathione levels even in HIV formulation. John James pointed out that this study may have been looking at the wrong levels according to the developers of the drug. The tat-protease drugs are moving very quickly. We need to make sure the process keeps moving along and that there are no problems w/ the pharmaceutical co.'s.

Michelle reported on Oncology. The fumagillin and antiangiogenesis drugs will open shared by the NCI and ACTG. The IL-4 designer is on top of protocol design even though the CS is not yet written. There is a new trial for anal neoplasia; PX of interferon/retinoid. There is a problem w/ the combo therapy of ddI/interferon trial in that the high dose of interferon is very toxic and raises quality of life issues. Michelle stressed the need for a national IRB. This was her last CCG as she is rolling off the cmte.

Linda Dee reported that the OI Cmte. needs restructuring. Some languishing protocols need to be closed. There was discussion of regional development of protocols where the specialists are. The group was divided over the issue, however it seems that this would prevent certain patients from gaining access to particular trials. Then we remember that trials are not Tx.

Jesse was not optimistic about the Immunology Cmte. There of course a problem w/ funding; PI's aren't interested in designing trials because there is no funds. He stated that the core mtg.s are too crowded and that the members can't concentrate and get their work done. The high tech trials seem to be a long way off. The Peg IL-2 trial looks good, needs to study it in combo. The vaccine GP-160 trials look good.

Reported by:
Matthew Sharp
800 Church St. #25
San Francisco, CA. 94114
(415)821-1096

Oncology- see my attached CCG report, done with Michelle Roland.

CCG notes

PETT Project: May work in connection with ARAC to arrange this project. The goal: to deliver up-to-date treatment information to affected populations. Possible outside funding: AMFAR, Hoffman-La Roche, Burroughs Wellcome.

KEMRON: CCG endorsed a proposal to have a new study of oral interferon, because of the stated desire of members of the African American Community.

INSURANCE: the issue of collecting some study expenses from third party payers was referred to a subcommittee of myself and Jonathan Wadleigh who will produce a report.

June ACTG is a closed retreat dealing with structure, organization and goals. The CCG adopted the following stands on closed meetings.

The CCG expects 3 open ACTG meetings per year.

The CCG supports the decision for this retreat alone to be closed.

Our CCG core meeting, at this retreat as always, will remain open.

C.A.B. Network: CAB budgets are already in effect at some sites. Sample budget was distributed. Funds come from local site. No new directive is to come, or any new funding. Sign up for National Working Groups! Concept sheets available from local sites per approved process. Interest in a CAB network meeting the first day of next December's ACTG (simultaneous with CCG's first day).

ACTG Plenary April 13, 1992

Larry Corey: Concepts in the therapy of HIV infection

Infection of hematopoietic, skin, G.I., many classes of cells. Peripheral circulation may not accurately represent actual body pool of HIV.

How are CD4 cells depleted? Perhaps toxic HIV gene product (gp160), syncytial formation... Possibly an auto-immune response: to region of IL 2, cell death by chronic activation.

All reverse transcriptase drugs do is to prevent the infection of new cells. We are NOT affecting already infected cells and their expression.

ACTG 002 showed 90% dead at 30months, with accelerated decline after 12 months. This looks to him like drug failure, clinical effect of AZT resistance.

How can we affect the EXPRESSIVE phase. Hope for TAT and Protease inhibitors. These also don't eradicate infected cells, but do block production.

T cells of 500 = 80% loss of body's immune mass. This is not early therapy!

Model for primary infection. Pig tailed macaque from Indonesia. Macaque Nemestrina.

UPDATE on ACTG 116B/117 Lagakos and Kahn

To be presented at FDA meeting.

2 levels of DDI compared to AZT in pts. with prior AZT

Trial population: 96% male, 82% white, 79% gay/bi

mostly t cells less than 200

p24 43% positive

median prior AZT 14 months

Treatment discontinuation. ddc 500 < ddc 750 < azt 600

Efficacy

	hi ddi	azt	low ddi
#	311	304	298
new oi/death	115	125	94
death	57	54	49

new oi	86	104	71
new/recurrent oi	94	113	81

at week 80 time to 1st new event low DDI > med ddi > azt
 time to new or recurring both ddi > azt
 but, time to death no difference

NOTE most deaths occurred more than 30 days after people stopped treatment; that might explain why there is no death difference. the ddi benefit was mostly seen in ARC patients. No difference in AIDS (but yes difference in KS pts..) While ddi is better in general, there is no increased effect for people with longer rather than shorter azt hx.

TOX

hematologic greater in azt

neuropathy NO difference

pancreatitis higher in ddi (esp hi dose)

MARKERS

cd4 at 1 year: cd4's drop 10 cells more on azt

50/50 (50 cell or 50% increase): criteria continued favorable to ddi

p24: high ddi has best effect up to 1 year statistical significance up to about 16 wks

COMPLIANCE

only 1 azt pt took ddi (noncompliant)

80% of ddi people showed ddi in urine analysis

azt people had high MCV's. ddi people dropped back to normal

treatment discontinuation may have lessened effect shown over time, and cause some false negative results (including no survival difference)

116A study (many naives) data pending

118 also. Last visits of both are done. Need to clean and complete data. Analysis will start in summer.

Off Site Meeting at F.D.A.

Dr. David Feigel
Dr. ?Hogel; Enforcements
Randy Wykoff Office of AIDS Coordination
Nancy Stanisic " " "

For DDC meeting, the FDA did not request ACTG to open up 155 efficacy data. Toxicity data for combo will be broken, at companies request. Above data from 116, 117 supports the use of surrogate markers in drug approval. One of the 4 new proposals announced by Quayle last week is for drug approval in AIDS based on surrogate markers; this includes requirement for post-marketing trials to validate clinical outcomes, and allows expedited withdrawal if a company does not act with "due diligence" to get this added data.

Other points included coordination with foreign governments, parallel track codified (but not changed a lot), and outside review option (for less serious diseases).

Discussed enforcement issues.

Off Site Meeting at Burroughs Wellcome

B-W brought about 20 activists to North Carolina to discuss our concerns with them. Included treatment and research activists, gay public officials, Community Based Organizations. (I have full list.) Impressive representation from B-W, including their US C.E.O., and director of research. Many issues discussed, no commitments made.

ACYCLOVIR- We asked them to lower price, perhaps just of the 800 mg. pills

BW566C80- They said reformulation, to be done in England, will take 6 - 9 more months. We asked for speed-up.

NEW DRUGS- They are working on more nucleoside analogues (same family as AZT DDI DDC). They have a small protease and TAT program, but sounds like they are letting other companies pursue this. They believe that improved nucleosides will be a major therapeutic advance.

FDA- We would like an activist to attend all meetings of FDA with B-W.

RESEARCH- Peter Staley asked B-W to contribute \$1 million/year x 5 years to support Community Based Clinical Trials through AMFAR.

COMMUNITY PROGRAMS- Various proposals for expanding education and access to clinical trials. Advising B-W on their "educational materials".

Off Site Meeting at National Cancer Institute

Dr. Schepartz and Tomaszewski

AGM-1470 development on track. Toxicities appear manageable at lower doses. Expect IND application end of June.

CCG ONCOLOGY COMMITTEE

April 1992 ACTG MEETING Report

Michelle Roland
and Andy Zysman

*Please refer to the attached interim report, letter to Tony Fauci, and
"Plea" flier for background information.*

1) ROLE OF THE ACTG IN ONCOLOGY RESEARCH

I (Michelle) distributed copies of my interim report, letter to Tony Fauci, and "Plea" flier, and had discussions regarding the role of the ACTG in Oncology research, with the following people: John Phair (E.C. chair), Dan Hoth (Director of DAIDS), Lew Barker (Assoc. Director, CRP, DAIDS), Giorgio Galetto (Medical Officer, DAIDS), Ellen Friedman (Medical Officer, NCI), Sandy Levine (Oncology Committee chair) and other members of the Oncology Core and Full Committees. I did hear back from Tony Fauci's office, and tentatively have a date to meet with him in May.

Although near the end of the meeting I felt completely defeated in my attempt to initiate a proactive planning process with ACTG, DAIDS and NCI folks regarding 1) a research agenda for HIV-associated malignancies and 2) assigning of appropriate mechanisms (ACTG, NCI-sponsored RFA/RFP, NCI-sponsored cooperative cancer groups, etc) to address mutually agreed upon research questions, John Phair did approach me at the final Plenary session and agreed that these were issues that required leadership from the Executive Committee and that he would provide such leadership. I felt a bit more hopeful after that brief exchange.

Why did I feel so defeated? Although the first item on the agenda of the Oncology Core Committee was discussion of the research agenda, that agenda item was skillfully avoided throughout the entire meeting. A great deal of productive hammering out of several concept sheets did occur during this meeting. However, the rare opportunity to use this time together to do this same kind of brainstorming about the research agenda and who should be studying what under which mechanism was missed. Given the timing of the June retreat and the impending issuance of a second RFA from the NCI, I felt that this was a crucial opportunity to initiate a planning process to make the June retreat time as efficient as possible. I did not vocalize my disappointment during this meeting. Why? I guess at that point I felt like I'd put myself out there, assertively talked to everyone I could think of, and maybe I was just missing the boat. I was tired of pushing and being the naive bad-guy. In reality, I think it's just a whole lot easier for everyone involved to go along as usual, haphazardly coming up with ideas and responding to the actions of others, rather than sitting down and really sweating it out for a few days (and the weeks and months of preparation and follow-up) to come up with a comprehensive and efficient plan.

So, where are we now with this issue? After long discussions with Dr. Galetto (medical officer), he agreed to follow up on my discussions with Lew Barker and John Phair. Dr. Barker had agreed to support (in concept) a meeting of ACTG, DAIDS and NCI folks for several days before the June retreat (and would look for funding) if the Oncology Committee requested such a meeting. Dr. Phair's statement of support during the Plenary probably needs to be followed up on if this support is to materialize. I will speak with Dr. Fauci. Then I let go of it...

Has anything positive happened in this area? Yes, Drs. Yarchoan and Pluda from the NCI attended the Onc. Core Meeting, were extremely open about jointly studying AGM-1470 (more below), and were asked to join the Core Committee. Ellen Friedman also attended the Oncology meetings. Small but important steps in the absolutely right direction...

Results from Ongoing Studies

2) Important Results of ACTG 094 (Chemotherapy in Lymphoma)

The interim results from this study demonstrate that the use of GM-CSF does NOT enable one to increase the dose of chemotherapy, because the dose of GM-CSF which is effective is not tolerable. These results were a bit surprising, and have important clinical implications, since many people use GM-CSF in this setting. G-CSF may be effective at tolerable doses, since it has fewer side effects. A concept sheet with G-CSF may be developed.

Concept Sheets in Development

3) IL-4 CS

Revisions to CS372R, a Phase I study of IL-4 in advanced KS, were discussed during the Core Committee meeting. Many of the changes I had suggested were taken into account, making this a less restrictive, more participant-friendly study design. Steve Miles, the author of this CS, is very experienced with the ACTG bureaucracy and had already written the actual protocol, so I expect this study to be opened to accrual relatively quickly. This type of proactive approach should be encouraged by all investigators. It would behoove us to encourage concept sheet authors to speak with experienced investigators like Steve Miles to get their advice about how to proceed through the ACTG system as efficiently as possible.

4) AGM-1470 (fumagillin analogue):

Drs. Yarchoan and Pluda from the NCI Intramural AIDS Program attended the Core meeting. They shared the information they had regarding the results of animal studies and production of the compound. They are in the process of writing a protocol for use at the NIH (late Spring or Summer) and were very supportive of the ACTG using either the same protocol or writing one using different dosages or routes of administration. Parkash Gill is working on a concept sheet and will consult with Yarchoan and Pluda to ensure that the protocols are compatible, so that useful comparisons can be made across the two studies, if it is decided to use two different protocols. Dr. Levine emphasized the need to ensure that this study, and others of exciting new agents, be open to as many sites as possible. The only potential problems in this area are 1) limited supply of the drug and 2) toxicity. The supply issue may require some pressure on the company. The NCI has agreed to ask Takeda to produce additional drug for an ACTG trial. Dr. Hill must provide a preliminary protocol and an estimation of quantity needed, and has been asked to do so.

5) Cervical/Anal Intraepithelial Neoplasia (CIN/AIN) Update:

There was a very long discussion about the AIN concept sheet using interferon and a retinoid. The upshot of that discussion, I think, is that a pilot study will be designed initially to look at the safety and efficacy of this regimen as *treatment*, before a prophylaxis trial is started. Look for the next version of the concept sheet...

There is still a fair amount of resentment at the Women's Health Committee for going ahead and developing the 5-FU protocol without incorporating an INF/Retinoid arm into the study (or at least discussing it more with the Oncology Committee after having indicated an interest). There is a temptation to continue along a competitive mode, holding on to "our" ideas, etc. I strongly urged the Oncology Core Committee to continue trying to work collaboratively with the Women's Health Committee, with the assumption that such collaborations will begin to work. I believe that continual community support for such collaborations, and reminders about the pitfalls of such competition, will be important in this area.

ACTG 200 5-FU to prevent recurrence of cervical dysplasia after appropriate treatment. Andy attended these team meetings and will contact Michelle Wilson to decide who will continue to follow this protocol (This is a Women's Health Committee protocol). Progress was made to make the enrollment criteria less restrictive. Now, women with recurrences of cervical dysplasia will be able to enroll (they were previously excluded).

Protocols in Development

6) ACTG 206 (ddI/INF in KS)

A near final draft of this protocol has just been distributed to the Core Committee and to the PES. I have not had a chance to review it, and will ask Andy to take on that task. The one suggestion I did make to Susan Krown, the protocol chair, is that she consider having a protocol neurologist and incorporating a brief neuropsychological assessment into the protocol. I suggested this because the ddI/INF combination caused some psychiatric side effects in participants in an intramural study (although at higher doses of interferon, I believe). Dr. Krown was afraid that adding such an assessment would make the trial less attractive (more time consuming) to participants. I'm not sure how valuable it might be, but I think consulting the neurology committee would be a good idea. Dr. Krown took my notes about this suggestion; Andy and Victor should probably follow up.

Ongoing Protocols

7) ACTG 163 Accrual Problems

This KS study of chemotherapy plus ddI or ddC is having accrual problems because there are few sites registered, some registered sites have not enrolled patients, some potential participants do not want to be randomized to ddI or ddC, etc. Recent changes (more sites registering) will probably improve accrual to the Phase I portion, after which a decision will need to be made about continuing to Phase II (and whether ddI, ddC or both will be included). The study chair asked me to write a letter to the CABs similar to the ACTG 142 letter, explaining the value and limitations of the study and asking for feedback and for "advertisement" of the study. Andy will write this letter after a protocol team conference call reviews the protocol in May.

8) ACTG 142 (Lymphoma, non-Hodgkin's) Update

Accrual is improving, slowly. Attempts to get one of the NCI-funded cooperative cancer groups (SWOG) to enroll patients seem to not be getting very far. The NCI agreed to give SWOG sites credit (important for renewing their contracts/grants), but no funding. It seems unlikely that the ACTG will be able to fund SWOG sites. Such collaborations are very important not just to increase the accrual in ACTG 142, but also 1) to involve oncologists

outside of the ACTG in treating people with AIDS (they need to be educated!) and 2) establish future proactive collaborations with the cooperative cancer groups.

9) ACTG 149 (Hodgkin's Lymphoma)

Because this type of lymphoma is so rare, it is guaranteed that it will be difficult to accrue this study. Sites are very reluctant to register because of the time-consuming process of getting IRB approval when they may see a single patient during the duration of the study. If this study is to be completed, the "community" will have to take an active role in letting doctors and patients know about it. Andy will write a letter to the CABs. Note: the chair of this study was, again, not present at the meeting. He is also seldom on telephone calls.

Research Ideas We Need to Consider Pursuing

10) CD8 Expansion and KS?

A small study of CD8 expansion plus IL-2 showed KS regression in two participants, raising the question about the utility of this approach in KS. I understand that a large primary infection study is being designed. This primary infection study should be designed up-front to look at the effect on KS. The Oncology Committee should participate in the design of the study. Andy and Mark will need to follow up on this.

11) TAT study

Again, this primary infection study should be designed up-front to look at the effect on KS. The Oncology Committee should participate in the design of the study. Andy and Mark will need to follow up on this.

12) Retinoids

Several ACTG Oncologists are either studying retinoids in KS (through NCI and/or drug company funding) or are using them in individual patients. Someone should be encouraged to assess the state of the knowledge in this area and what role the ACTG can play in studying these compounds. A concept sheet author is needed...

MISCELLANEOUS ISSUES

13) National IRB

The ACTG needs a national IRB which would approve studies for all the participating sites. Otherwise, we will continue to have sites not participating in studies simply because the IRB process is too time-consuming, especially for studies of the less common manifestations of HIV.

14) Incentive Funding

The oncologists are concerned that ranking for incentive funding will not take into account the time-intensive nature of the Oncology studies, but will look only at the quantity of data generated. They expressed a concern that if there is an Executive Committee Working Group on this issue, it should have oncology representation. Several investigators offered to track the amount of time spent with individual study participants in a few of the Oncology studies in order to support their belief that these studies are time intensive.

15) Bye!

This was my last meeting. Andy is the new CCG Oncology Representative. Please feel free to continue calling me, asking for my perspective, utilizing the relationships I have established with ACTG investigators and DIADS staff, etc. I will not always be available, but you can always ask, and if I'm too busy I'll let you know.

CCG members: I WILL MISS YOU! In spite of the struggles and frustrations, or perhaps because of them, I have grown very fond of this group. I'll miss working with "The CCG," but I'll especially miss you each individually. Please stay in touch and good luck...

Protocols with Accrual Problems

- 1) ACTG 147. See above. Improving. Ongoing issue with SWOG collaboration.
- 2) ACTG 163. See above. Andy will write letter. Need to monitor Phase II.
- 3) ACTG 149. See above. Will require education patients and physicians in the community when open to accrual. Andy will write letter.

No action required by the Protocol Development Subcommittee on any of these studies specifically. The National IRB issue does need to be attacked somewhere if we want more sites to participate (and we do).

ACTG REPORTBACKS - Virg. E. Parks

Focus: Women's Issues

Explanation of reportback structure: Since several Women's Committee meetings covered the same topics and trials, I've tried to consolidate the information regarding epidemiology and accrual of women and am presenting my overall impression. I've done the same with the pediatric protocols I covered. (I only covered pediatrics meetings that Vince was unable to attend or were combined with the women's committee)

- I. Accrual, Epidemiology, and Studies
- II. ACTG 200
- III. Pediatrics
 - A. Patient Care Working Group
 - B. Vaccines
 - C. Protocols
- IV. Miscellaneous
 - A. Community Consortium Group (notes from first day's meeting)
 - B. Statistical Working Group

EPIDEMIOLOGY, ACCRUAL AND STUDIES

The good news: The ACTG is beginning to ask questions like: Why aren't more women accrued? Why are most women accrued white, upper-income and well-educated? What are the restrictions keeping women out of trials?

The bad news: They don't seem to have the answers.

Due to very low accrual in 175 and the fact that 019 accounts for 30% of all women accrued, if 019 isn't included there are not enough numbers for statistical power. Low accrual numbers also creates a catch-22 situation with the CDC definition. CDC: "There aren't enough statistics to know what women specific OI's to look for"...ACTIVISTS: "How the hell are we going to know what OI's women get most often if women aren't diagnosed earlier and followed more closely?" The Women's Epidemiology Working Group sent a letter to the CDC essentially suggesting the following: (1) Include CD4 counts in definition (2) keep current OI's and expand to include women specific (gyn.) OI's (3) combination of both.

At the Women's Gynecology/Oncology/Endocrine Working Group meeting, much of the focus was also on accrual. Some ideas and suggestions which came out of this meeting:

As women become aware that their "special needs" are being considered, accrual will be better. We need to start getting women into ACTG sites now in anticipation of more gyn. trials. Perhaps incentive or extra funding for women's studies. Women's studies come from a separate pot of money, but should be an integral part of ACTGs. Each ACTU should have a liaison with OB/GYN's.

ACTG is an investigator initiated program. ACTG CAN find the money, but investigators MUST bring more women specific concept sheets.

Women's committee is looking at barriers, such as childcare, transportation, different lab variables, etc. Also asking investigators on all trials to more aggressively seek women to enroll. Asking investigators to do a gynecology history form on ALL women accrued whether it is a women specific trial or not.

Question asked by an HIV+ woman: If so much money is available, why was the study in Cincinnati closed to women? (not sure what study she was referring to). ANSWER: ACTG 200 is the first truly women specific protocol. In the past, protocols have focused on patients with low CD4 counts but now beginning to look at earlier intervention. (now did this answer really answer her question??)

Another question from the audience: What about women who have no insurance and don't follow-up on treatments for lack of money? ANSWER: Healthcare funding varies from state-to-state...seek out resources in her state. (once again, a lame answer...I told her afterward about the ADP and suggested she try to find out what IS available in her state...if it's a short list, organize and try to make it longer and more accessible...also told her about WORLD...I was bummed that I didn't see the woman with the first question later to turn her onto WORLD as well...)

Also discussed at this meeting: HIV-related ulcers (vaginal) which seem to respond to anti-virals, herpes which sometimes responds, and syphilis - we need better treatments than currently available.

SURVEYS - Notes from Accrual and Polysubstance Abuse Working Group and Women's Health Committee Full Committee

Both studies were "quick and dirty"- faster and therefore perhaps not as efficient and detailed - but by not going through the ACTG as an official protocol they can expedite getting the info. My understanding was that both are still incomplete.

Polysubstance Survey looks at women drug users. (I was glad they used the term "users" instead of "abusers") Women tend to use more than just IV drugs. But other substances (like alcohol, which is 2nd most used) also keep women out of studies. We need to develop strategies which will not only get women IN trials but keep them in trials. Re-evaluate restrictions keeping drug users out of clinical trials.

Accrual Study's objective was to provide a snapshot of why (or why not) women enroll in trials. Also to develop potential strategies. A questionnaire was sent to all ACTU's. Approximately 65% responded. Response was voluntary, so sites with low enrollment of women (of course) didn't respond. SOME OF THE QUESTIONS ASKED: Does site provide primary care? What does the site offer (ie: daycare, transportation, social worker, etc.) What is the site's network (CBO's, CAB, city health department, etc.)? FACTORS POSITIVELY ASSOCIATED WITH ENROLLMENT OF WOMEN: Social Worker, Support Group specifically for ACTG participants, Buddy System, Staff Support helping women access food stamps, childcare, transportation, referrals, etc.

Results of these two studies weren't published yet, and unavailable at the ACTG's but

I'm trying to access them and will feed you more later.

Debra Cotton reported (at the Full Committee meeting) on stats derived on women from overall ACTG trials. Elimination of 019 made a huge difference in the overall study outcome. OBJECTIVES of the study: Estimate baseline characteristics, compare progression of CD4 counts, compare toxicity rates, compare dose reduction, compare mono-vs-combo therapy, compare drop-out rates. SOME RESULTING INFO: No large difference in toxicity and efficacy, but if greater numbers, this information could prove useful in answering specific questions like studying common toxicity and CD4 counts. Numbers weren't great enough to determine subtle gender differences in toxicity and efficacy. Most women accrued were white and non-IVDU's. Geographically, if an area had fewer percentage of HIV+ women the sites were able to access the women better (why? wasn't answered). Currently only 10% average accrual (overall, less than 7%)...SHOULD BE 15-20% women accrued in studies more in line with percentage of women with HIV.

ACTG-200 -- FIRST GYN PROTOCOL IN DEVELOPMENT

Fluorouracil (5-FU) as a prophylaxis in treating cervical dysplasia

5-FU is currently a common treatment for genital warts. Cervical Dysplasia is a precancerous condition seen when a pap smear indicates abnormal cell growth. A pap might show CIN I, CIN II, CIN III, etc...the larger the number indicates increased cell growth. What usually happens when a woman has an abnormal pap result is that she's referred a colposcopy. An instrument called a colposcope is used to look more closely at the woman's cervix, vaginal walls, and vulva. Small biopsies are taken and sent for pathology. If the dysplasia is very advanced, she should have a cone biopsy. The abnormal cells are then destroyed with usually cryotherapy (freezing) or laser.

What this has to do with AIDS is that women with HIV appear to have a greater tendency to experience recurring dysplasia and with greater severity. It seems logical that women with HIV would also experience faster growth of abnormal cells indicating a need for more frequent pap smears. Generally, cervical dysplasia progresses relatively slowly (over a one year period, CIN I might progress to CIN II in an HIV- woman) but since there isn't alot of research out on women, I don't know how quickly it progresses in HIV+ women. Perhaps this study will answer that question.

The objective of the study is to determine if 5-FU would be an effective prophylaxis for cervical dysplasia. There are two arms in the study: a TREATMENT ARM in which the woman (who's dysplasia has been "cured") self-medicates with 5-FU every two weeks over a 6 month period returning every 2 months for a follow-up exam - and an OBSERVATIONAL ARM in which the woman is treated one time with 5-FU and then observed over a 6 month period with bi-month exams. There is no placebo since the side-effects (burning, etc.) are virtually impossible to duplicate.

Originally, the protocol excluded women who had a previous episode of cervical dysplasia and women who should have had a cone biopsy but were referred for a colpo instead due to medical mismanagement. Andy pointed out that since the community best served by this treatment ARE women with recurring dysplasia, they

should not be excluded. I pointed out that women also shouldn't be excluded because of their doctor's error. What came of this is that women with recurring dysplasia WILL be included and separate data kept on them. Women who should have had a cone biopsy will be referred for one, the dysplasia treated, and then they CAN enter the study. At a later meeting it was suggested that the observational arm allowed no incentive for compliance, since if the woman had reoccurrence she would be dropped from the trial - and that instead there should be cross-over to the treatment arm. The statistician was thrilled beyond words with that suggestion but left with a promise to try to make it work -- even if it means extending the length of the study.

Other issues that came up: STD screening since active cervicitis or chlamydia could increase the possibility of toxicity - this would not be exclusionary but the data is needed. If mucosal lesions develop, patient would be taken off treatment until lesions heal, then resume 5-FU. The pathologist on the team suggested cervical HIV cultures for the additional data that could provide (sort of ...well, while yer down there...you may as well find out all you can...) and the rest of the team agreed. What seemed possibly their most difficult problem was how to access if prior dysplasia treatment was adequate without doing a second colpo (not all sites have colposcopes) and do so with some consistency from site to site.

PEDIATRICS

PATIENT CARE WORKING GROUP - PEDIATRICS

(Women's Patient Care Working Group was canceled/combined with Peds)

A survey was done of patient care workers. Most did scheduling, writing consent forms, phone triage, alot of clerical, direct patient care, etc. Only one had anything with budgeting. Virtually ALL stated that direct patient care was the best part of their jobs. Most did NOT like all the paperwork associated with ACTG trials.

Investigators from one site (sorry, not sure which) presented some "Patient Compliance Forms" they'd developed for 076 and seemed pretty successful with in regards to helping keep women in the study. There were 8 different forms (no wonder they all hate the paper chase!) but the 4 which impacted me the most were:

Observational Data Base Form on which they tried to keep follow-up info. including the women who dropped-out.

Compliance Survey Form which asks psycho/social questions which may indicate potential non-compliance or drop-out tendencies.

Patient Compliance Form - a section for the staff to complete as well as a section for the patient to complete indicating what she liked/disliked, why she missed appointments or dropped-out, etc. The found that patients who didn't bond with staff are also more likely to drop out.

Pediatric Enhancement Form - asks the question "What would this particular patient need to keep them in the study?" Often the answers were little things which they phrased "gifts of love"...ie: new gown for hospital, maternity bra or other clothing, lunch vouchers, bus tokens, etc...especially useful with low-income patients. One site arranged housing and phone for a patient. It was pointed out that alot of the gifts

could be donated.

I got the impression that these folks sincerely cared about their patients and considered them PATIENTS not simply study subjects - even though the forms were developed and presented in a very scientific manner. I'd make bets that their patient-care "attitude" had as much (or more) to do with compliance than the forms. It seems advantageous to carry this attitude into all trials not just those involving women and pediatrics.

Also presented in this meeting was a video created to enhance the consent form for 076. To ensure that patients were giving an "informed" consent. I had a problem with the "informed" part because the video seemed to focus more on the process of the trial and potential toxicity was glossed-over. I also felt that the cartoon figures of AZT vs. placebo (in which AZT was a super-hero type persona) was a bit condescending. However, when asked about that, clinic staff indicated that they'd had no such reaction from the study participants and found them very useful. Several of us addressed the issue of English being the only version and were met with several reasons why a Spanish version could not be done. Main opposition was financial. It was suggested that it wouldn't cost much to simply over-dub the existing video or seek-out a (perhaps hispanic-owned?) video production company to donate the services. A member of the CCG "representing the black community" (whom I won't name) said that overdubbing would not suffice...that totally new community specific versions featuring Hispanic or black actors would be required. WHY do folks always have to complicate simple answers? We left that meeting without the impression that anyone planned to address this issue at their sites. This is something I'd like to follow-up on.

PEDIATRIC VACCINES WORKING GROUP

Currently, there are several different vaccines being considered and a specific protocol has not yet been written for a pediatric vaccine trial. The master protocol would probably be a Phase 1 toxicity study in Pediatric age group 1 (infants known to be infected). Then more safety studies in P-0's (newborns). THEN go into efficacy trials.

Start-up seems pretty distant, since before they do this, they still need to: write the protocol(s), choose the vaccine(s), and choose endpoints. Plan for efficacy trials would probably involve two different protocols begun simultaneously (with arms determined by age group)

CONSIDERATIONS WHEN DEVELOPING PROTOCOL:

What kind of criteria would be used to include or exclude?

How would children's ages be grouped?

Order of vaccine focus? Pregnant women, then older children, then infants?

Or simultaneously (this seems more logical)?

6000 women with HIV are giving birth per year with only an estimated 1800 response to clinical trials. Many of these will already have been accrued into ACTG-076 or ACTG-185. They hope to get 25% of the estimated 6000 into a vaccine trial. It is important to identify HIV+ mothers before labor (not happening now)

According to one of the researchers, there is supposed to be an adult vaccine

trial which allows pregnant women. I asked the P.I. (after the meeting) if the mother participated in an adult vaccine trial, would that affect the inclusion of the infant in a pediatric vaccine trial? (women in 076 and 185 would be excluded from pediatric vaccine trial) He said that was something they'd not yet considered by should.

MISC. CONCERNS, QUESTIONS, & CONSIDERATIONS:

Vaccine discussion brings up 2 different issues: prevention & therapy.

Remember immunizational theory/history: we vaccinate newborns with alot antigens with good response. Check to see if children respond to other vaccines?

Immunizing known HIV+ children could bring valuable information on efficacy.

Immunizing newborns could provide data on prophylaxis. (But not so reliable...would they have been negative anyway?)

Can't extrapolate this info. from adult data because infant immune system is different. This is a chance to prevent transmission in a high-risk group. In older children, more likely to repeat same as adult data. (However, we don't KNOW that immune response in older children/adolescents isn't different, because we have so very little data on this group...less so than with women)

Difficult to develop in-utero vaccine because we still don't know for certain how and where transmission actually occurs. If infected in-utero, than it would be wise to vaccinate Mom. If transmission occurs during delivery, it would be more effective to vaccinate newborn.

Toxicity studies can provide a base for vaccine against different strains.

ACTG-153 INVESTIGATORS MEETING

AZT vs. Alpha Interferon and AZT vs. Alpha Interferon in Peds.

This was a very confusing discussion of toxicity and cross-over. At least I wasn't the only person confused...so were most of the investigators. So here's what I gathered:

This is a Phase I toxicity study in infants...usual process would be (1) all 4 infants do AZT for 4 weeks, then (2) all move to Stage II, Alpha-Interferon with AZT - with 2nd arm of 4 on high-dose Alpha-Interferon. However, they seem to be having problems with toxicity grades and protocol interruption. AER grades are being challenged and there is concern over Grade 2 toxicity indicators. Currently, the protocol says to stop drug, wait for resolution, and then start again. Would stop and start 3 times, but they're changing the protocol to stop and start only twice. If a child goes from AZT to AZT plus alpha-interferon and develops toxicity, then the child would be replaced by one from the Alpha-interferon arm and see if this child develops toxicity...then they'd have the maximum tolerated dosage. Questions arose over whether the child dropped from AZT/Alpha-Interferon combo would be dropped from the trial all together. There is also a mechanism in place to stop enrollment if toxicity is present and start over at lower dosage.

ACTG-185 TEAM MEETING

Pediatric IVIG vs. HIVIG in stopping vertical transmission

This study also seems to be an exercise in frustration for the researchers, activists, and study participants. Not only is Abbott being totally uncooperative about supplying the HIVIG but some good suggestions presented by researchers and activists seem to be complicated by the restraints of working in a bureaucratic system -- such as:

Increasing coordination between competing studies at sites...if more than one natural history study is being done, why not coordinate the lab visits and run both studies off one blood draw? The ACTG is however, often very strict about which protocols can be exempted on duplicate labwork. (on I believe the first or second visit, 17cc of blood is drawn...ALOT for an infant)

Extended phenotypes -- with NICHD funding -- any NAIAD or ACTG sites who wish can participate in providing normal lab data on study infants...will possibly allow insite into devmt of new markers and help in earlier diagnosis (ratio for CD4 subset of naive and mature cells are shifted...infected children will have fewer mature cells) .

To date, there aren't established normal ranges on (uninfected) infants. If they (185 research team) could get samples (or lab results) on uninfected babies, they could establish normal newborn infant lab variables. Problem with getting samples and storing or transporting them is that some of the lab needs to be performed on a fresh sample. Problem with simply doing the lab at the clinic where drawn or some other more expedient manner is the same ol' story...funding.

These are all complications which can probably be worked out because the team on 185 is highly motivated. (The consent form is already translated into spanish). The BIG problem right now is ABBOTT.

ACTG 076 - Some early results

98 women enrolled...62 babies born...mother's median age: 26...median CD4 counts: 580...all adverse events were natural complications of pregnancy...grade 3-4 toxicity evenly divided in infants by group...no serious toxicity seen in women... follow-up on mother at 6 weeks and 6 months...regardless of randomization, all women with less than 200 CD4 counts get AZT .

NEW CONCEPT SHEET is being developed which will study the efficacy of adding CD4-IgG intrapartum/perinatal and on neonatal infant -vs.- AZT administered the same -vs.- a combination of both. Women would need to be 34-36 weeks gestation therefore not conflicting with 076 or 185 (which need to be pre-34 weeks). Women who refuse 076 or 185 would also be offered this as an option. Also not closed to women already on an anti-viral. *Problem:* now that more trials are becoming available, women should be advised of ALL protocol options...ie: if a woman at 32 weeks qualifies for 076 or 185 the site isn't required to advise her that she could wait 2 weeks and enter a different study. *Solution:* real informed consent.

MONDAY COMMUNITY CONSTITUENCY COMMITTEE MEETING

COMMITTEE REPORTBACKS

Executive Committee - CAB sent questionnaire mailing to P.I.'s regarding barriers to access. (see my notes under Accrual) Developing a data share policy. Currently information is only released to the FDA, not pharmaceuticals. Overall strategy - scientific committees should all submit agendas to exec. committee. Executive committee will have liaison to each scientific committee. Also suggested: less overlap of meetings (I'd like that!) and more combined meetings. During recompetition, 8 sites were cut...then Fauci "found" some extra money and refunded all but one through 1992...so, what then? That question, as well as exactly where did the money come from? where never properly answered...also, sites that were funded had they're budgets slashed. Sites are being encouraged both to enroll more (getting more funding that way) but also to enroll fewer (to save funds)...considering Incentive funding whereby sites accruing more people of color, women, etc. will receive more funding. Report from the 2/25/92 exec. committee meeting: Most (especially researchers) want the closed committees open. One investigator ACTG-076 has ethical concerns that there is no longterm follow-up on the women. This was recommended by the Data and Safety Monitoring Board. Questioned what the specific roles of the protocol team members are. John Fare, new exec. head seems to be a good influence.

O.I. Committee - Encouraging more input from the community and more O.I. trials for women.

Immunology Committee - Restructured into 9 groups. Surrogate marker working group is encouraging collaboration between virology, immunology, and primary infection committees. Pediatric trial (#152) measuring beta 2, soluble CDH, theoptrin (sp?) has been approved. It was mentioned that at 3 sites, the individual sites are paying for all their own labwork...why?

Pediatrics - For details, see mine and Vince's reportbacks. Peds committee has divided into 9 working groups. One of which is focusing on adolescents (about time!) ACTG #369 is videotaping children to evaluate psychosocial changes in children with HIV (nested study).

Oncology Committee - Questioning what IS the role of the ACTG? And perhaps moving toward letting NCI take leadership. (see Andy's reportback)

Virology Committee - planning 4 new concept sheets - one pediatric. Possible rationale for slow-down on CMV-oral gancyclovir trial: Syntex seems not very well organized and not aggressive about development or meeting with the community, only one factory and in self-competition (oral vs. IV), also possibly collaboration between Syntex and home healthcare companies (which of course would want to keep it only IV). In ACTG-175, 900 accrued but most sites seem to be having a difficult time with finding AZT naive patients. Sites whose communities are primarily people of color are having an especially difficult time. (see G'dali's reportback)

Membership Committee was accepting new applications for the CCG. By the time you read this though, it'll be a done deal.

Pharmacology Committee has submitted a concept sheet for TAT inhibitor and AZT (CS #386)

Patient Care Committee reported that the Hemophilia Network was encouraged to accrue patients then the study was canceled (not certain which study he was referring to). Mentioned a recent CDC report that there was a new seroconversion in a child who supposedly never got infected blood products (both have hemophilia) and are questioning if his brother infected him??? More likely answer is that the blood sterilization procedure broke down because otherwise, it would imply casual infection which is directly opposite everything we know regarding transmission. DNA techniques have determined that he shows the same viral strain...but if strains are a geographic thing, then that proves nothing...also several articles are coming out discrediting DNA testing altogether. RE: non-traditional and alternative treatments, Senate has called for ACTG to establish a panel to look into such studies.

Neurology Committee - (see Matt Chappel's reportback) - Seems like this committee is having serious communication problems. Delays in ACTG 175 nested studies and more efforts are going into ACTG 193 nested studies. Looking into using gancyclovir for CMV polyradiculopathy and nerve-growth factors for peripheral neuropathy.

Women's Committee - read my other notes...okay??

Accrual Subcommittee looks at accrual by site and accrual by protocol. ACTG is helpful in supplying figures, but community population breakdowns, especially determining percentage of AIDS cases and each ACTU's racial and gender breakdowns. Inappropriate to simply recruit people of color to fulfill the protocol target number. They must be educated and have truly informed consent. People of color appear to be a larger percentage in Phase I trials and under reported in Phase II and III trials. However, some Phase I studies are desirable.

Protocol Development Committee - Policy and format change suggestions: (1) Interim reports in writing (2) Accrual problems with protocols and what is needed should be written from perspective of priorities. Jesse Dobson will be point person from committee reports and update CCG priorities (3) National Working Groups - people on CAB's should sign-up. Another letter going out soon. (4) follow-up on protocols with accrual problems. (5) With more CAB members (not on CCG) on protocol teams, CCG needs more conference calls and correspondence to get all current information disseminated. (6) more CCG members need to be working on pediatrics.

PETT Project - Focus has been setting-up teams. In the interim, plan more than one meeting regarding outside funding. There is currently a small amount of money which could be used for PETT activities. Meeting with office of communications to get info to underserved communities in a way which is culturally sensitive and addresses special needs. How can PETT become part of the next fiscal year budget to get money for dissemination of info. Can PETT access funds from current fiscal budget? Or money from other compatible agencies? Set-up mechanism to access non-government funding sources. Goal: develop cost-effective mechanism for transfer of info (a) phone conferences and mailing to CO's, etc. (b) everyone agrees this is needed but how? ARAC endorsed concept of PETT, their objectives are in line with PETT's -- Translation of consent form (etc) of 175 into Spanish? Institution conducting the trial has the responsibility to provide consent forms in a language the patients can

understand. A standard form is provided, but altered accordingly to each community. (this sounds like bullshit to me...something would be better than nothing...and should be done by PETT)

MEETING WITH JOHN FARE

Goals: (1) Orient new units, especially new pediatric units. (2) Initial process of review of where we're at now. Retreat in June will include scientific committees. Entire structure should be reviewed.

Question: Scientific committees are setting priorities, CCG is setting priorities and institutional escellon is setting priorities all simultaneously. Better communication needs to exist. CCG needs to be aware of though-process before execu. committee issues new structure in June/July. Answer: Exec. committee will try to do so.

Q: Accrual in 175 and minority representation? A: 175 won't be the last large protocol. Wanting a master protocol to which arms can be added as needed.

Q: What about funding which comes from Congress and other higher-ups? A: Educated legislators (kinda a lame answer huh?)

Q: Incentive funds are not a solution to overall budget cuts. A: Executive committee acknowledges the problem.

Q: 10 sites not cut in recompetition due to political bias? How will esec committee address perception of stranglehold on antivirals? A: Inclusion and cuts were based on which sites they though would be most successful. Hopefully, he can dispel this perception. No sacred cows.

STATISTICAL WORKING GROUP

SURVIVAL vs. SEROMARKERS

With longterm follow-up you get better stats on early intervention. Relevancy of a short study follow-up decreases as time goes by. A good cohort study = participants who would try all different treatments. Longterm follow-up needs to have same statistical base as the original study. What is a clinical meaningful difference? Is it biologically feasible? Survival would be less expensive to track. Question isn't how long, but how intensive. Survival as endpoint is most reliable. However, people die of things other than AIDS. 50% of the VA study deaths were not HIV related. What kind of extra resources would be needed to do adequate follow-up? Other concerns: confidentiality, interpretation. One researcher suggested it would be no big deal to follow-up on patients, just a phone call or two every 6 months. There needs to be a well-defined goal for longterm follow-up then design the "perfect" form.