

621-3606
S.F. Central

Richard P. [unclear]

* Send to [unclear]
cc Joe Cowan -
Box 0986 -

OL Nurses

cc: Chief of Police
(Bob Reising)

for
9/5/91
141

**Why is UC
Medical Center
KILLING BABIES ?
For Science ?
Or for \$\$\$?**

**Stop the injection of placebos into
babies and children with AIDS !**

ACT UP!

Saturday, June 17 at 12 Noon

UCSF Medical Center,

505 Parnassus

**CHILDREN WITH AIDS, MANY OF THEM CHILDREN OF COLOR,
ARE NOT GUINEAU PIGS;
THEY DESERVE TREATMENT, NOT GENOCIDE!**

For Information, Call ACT UP at 563-0724

ivig2

6/14/89

To: Participants at the June 17th meeting with Act Up and UCSF
 From: Michelle Roland, member Act Up Treatment Issues Committee
 Date: June 17, 1989

Some further elucidation of the points raised in the letter from Hank Wilson, dated 6/13/89

1. Use of a placebo in children facing a life-threatening disease.

A. Is it ethical, in the context of a life-threatening disease, to withhold **potentially effective** treatments from people with the disease if they want to try it, aware that it has not been proven effective and has some toxicity associated with it?

B. If a parent wanted access to IVIG and was not willing to take the risk of receiving the placebo instead of the IVIG, would the physician prescribe IVIG for the patient, even if the child was eligible for the trial? If not, because of the existence of the clinical trial, then parents are essentially forced into entering the trial if they want their children to have some chance of receiving the treatment. The argument may be given that it would be impossible to enroll people in clinical trials with placebos if this option was left open (of course, this case is unusual because the drug is currently approved). My argument in response to this argument is that clinical trials must be designed so they meet the needs of individual subject/patients. If they meet these needs by offering the treatment to all participants who want it, there won't be a problem getting people to enter clinical trials

2. Use of a placebo when non-placebo alternative exist.

A. We are aware that the double blind placebo controlled trial is the gold standard in American research. We are also aware that alternatives exist and that there is significant controversy about the efficacy of placebo controlled RCTs, natural history controls, standard treatment controls, etc. We are aware that the alternatives we present are not ideal, however we think the benefits of non-placebo controlled trials outweigh the risks and we challenge the medical and scientific communities to work with people with HIV infection and their advocates to design ethical and scientifically sound trials.

B. In the specific case of IVIG, we offer the following alternatives:

1. Historical controls. Look at average numbers and types of infections, life span, etc. in children who have not received the treatment and compare these factors to children who are being treated. Pick your controls carefully so that comparisons can be made validly.

2. Current no treatment or alternative treatment (e.g. AZT) controls. The important distinction here is that people be given the choice of which, if any, treatment they want to use. Some people will choose not to try an experimental treatment, or one, like IVIG, that has some significant risks and discomfort

ivig2

6/14/89

associated with it. The arguments immediately arise about selection bias and reporting bias. Devise methods to minimize the reporting bias by what types of markers are compared. Devise methods to identify any significant selection biases and control for them in data analysis.

3. Use of IV placebo with potential for infection in children who may already be immune suppressed.

A. It seems unconscionable to expose immune suppressed children to increased risk of infection by giving them an IV placebo. Two arguments have been put forth. the first is that any local infections caused by the administration of IVIG must be controlled for in order to determine the safety and efficacy of the drug itself. My argument is that the method of administration is, in a case like this, part of what needs to be examined for safety. If you control out local infections, that important information is lost in trying to weigh the risks and benefits of the treatment.

B. The second argument is that no treatment controls would also be exposed to risk of local infection if they had their blood drawn as often as those children who received the drug. This is a good argument. I do not know, but would like to discuss if there are differences in risk between a needle stick for blood draw and an IV placement which stays in place for several hours. If so, then this argument is weakened.

4. Use of a placebo which is unpleasant and stressful. This stress may be immunosuppressive.

There is growing acceptance of the detrimental physical effects of emotional stress. The field of psychoneuroimmunology is examining the relationship between stress and immune function. Both animal and human studies have shown detrimental effects on immune function during or following stress. The stress of an IV may be outweighed by the potential benefits of the drug. Surely it cannot be outweighed by a placebo, even if the child is given excellent care and attention during hospital visits. This factor must be considered when analyzing the emotional and physical benefits of the placebo effect.

5. Endpoints.

A. In our discussion with physicians and others at Children's Hospital in Oakland, we were shocked that they were unable to answer our questions about end-point with other than the response of "2 years." Two years is the length of the trial, not the definition of the endpoints. They have agreed to respond to this concern and tell us if death is the endpoint. If it is, we believe that they will work with us to find much less severe and life-threatening end points.

B. The description of protocol 051 provided by NIAID states, "Patients are followed for the development of **serious bacterial**

ivig2

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infections, as well as for a number of factors relating to safety, tolerance, progression of disease and **survival**" (my emphasis). The frightening implications is that endpoints short of death and serious illness are not defined. If this is so, the end points of this trial must be changed.

C. At what point of illness is a patient/subject's status unblinded? Does the patient have the option of receiving the IVIG if s/he had been receiving the placebo? Will the study continue to pay for the drug and medical care in this case?

6. **AZT intolerance.** Since protocol 051 includes AZT, we are concerned about the issue of AZT intolerance. What happens to children who can't tolerate AZT? Are they given the opportunity to receive IVIG without AZT? Is AZT tolerance determined before the study begins. If not, is it followed closely during the study? Is AZT intolerance factored into the data analysis. Are the AZT intolerant discriminated against in a sense in this study if they don't have alternative access to the IVIG that is affordable?

6/13/89

To: Human Research Committee
UCSF

From: Hank Wilson

Member of ACT UP Treatment Issues Committee

Subject: IVIG Protocol 051 and 045

The Treatment Issues Committee of ACT UP wishes to meet with the Human Research Committee to discuss the IVIG Protocol 051 and 045. It is my understanding that committee member Ric Puglia sent a letter protesting the IVIG trial and requesting a meeting with your Human Research Committee. To date, we have had no reply. I have called Dr. Weintraub but my calls were not returned.

We are concerned with several issues:

1. Use of a placebo in children facing a life threatening disease.
2. Use of a placebo when non placebo alternatives exist.
3. Use of an IV placebo with potential for infection in children who may already be immunosuppressed.
4. Use of a placebo which is unpleasant and stressful which may suppress immune function.
5. Endpoints. Are the endpoints specified? Do the endpoints provide for unblinding the status of a particular participant's status if the participant's health declines? Is crossover to getting the drug allowed for placebo recipients if their health declines?
6. AZT intolerance. Is AZT toleration determined? Prior to the start of the trial? Are their endpoints for administration of AZT?

I have attached the Wall Street Journal article on IVIG placebo trials. We share concerns raised in the article. You are aware of the protest ACT UP has called for June 17. A meeting may help to establish the facts and resolve, clarify some of the concerns we have with IVIG placebo trials. ACT UP and our Treatment Issues Committee is diverse in terms of background and training and expertise in medical and AIDS research matters. We are similar in our concern for children with AIDS and HIV.

I may be reached at [REDACTED] and committee member Michelle Roland may be reached at [REDACTED].

Thankyou for your consideration.

Hank Wilson

Hank Wilson

[REDACTED]

the data center of metals distributor A.M. Castle & Co. underwater. An earthquake that shook Los Angeles in October knocked out computer equipment at California Federal Savings and Loan Association.

Most businesses are ill-prepared to cope with electronic disasters, computer and communications specialists say. That's partly because computers have crept grad-

panies are Comdisco Disaster Recovery Services Inc., a unit of Comdisco Inc., Rosemont, Ill., and SunGard Recovery Services, a unit of SunGard Data Systems Inc., Wayne, Pa. They have nearly 1,500 clients between them, including Chase Manhattan Corp., First Chicago Corp., PepsiCo Inc. and Harlequin Enterprises Inc., the publisher of romance novels.

increased the bank's exposure to fraud, because tellers only had time to check transactions of more than \$500.

But the bank's problems lasted only three days. Had they extended through its busiest period, on Friday and Saturday, "we probably would have had a mutiny on our hands," Mr. Hackett says. "We truly are a creature of the electronic age."

Critics Protest Use of Placebo in Testing Drug Therapy for Kids Who Have AIDS

By MARILYN CHASE

Staff Reporter of THE WALL STREET JOURNAL
The wrenching ethical debate over the use of placebos in testing AIDS therapies has moved into the pediatric ward.

Two years ago, the medical community was racked by protests over placebo trials of the drug azidothymidine, or AZT. Now the National Institutes of Health is drawing fire as it recruits some 400 children with acquired immune deficiency syndrome to help test an experimental intravenous treatment. Each month, at one of 30 or so hospital centers around the country, half of the children will receive a potentially helpful infusion of human antibodies; the others will get albumin, the chemical equivalent of egg white.

"These children (on placebo) will surely die during the course of the experiment," asserts Mathilde Krim, a biologist and founding chairwoman of the American Foundation for AIDS Research, noting that the children's average two-year life expectancy matches the length of the test. "It's like giving up on them." (Researchers strenuously disagree.)

The drug being tested is intravenous gamma globulin, known as IVIG, which is made from pooled human serum containing antibodies to a variety of microbes. The question is whether it can prevent bacterial infections causing sepsis (blood infection), meningitis and pneumonia, which often strike children with AIDS. Though the official number of such children today is 1,000, as many as 3,000 are feared sick, and it's estimated another 20,000 will be infected with the AIDS virus by 1991.

Promising Signs

IVIG is already an approved treatment for a variety of conditions, including other childhood immune deficiencies, and it is available to AIDS patients at a number of clinics. While it won't cure children of AIDS, preliminary studies suggest it could make them more comfortable and perhaps help them to live longer. However, a large-scale, formal test like NIH's is needed to prove its safety and effectiveness, says Anne Willoughby, co-director of the study.

The promising signs were seen several years ago in pilot studies performed by a pair of AIDS specialists—Arye Rubenstein of Albert Einstein College of Medicine in New York, and James Oleske of Children's Hospital of New Jersey, in Newark. Dr. Rubenstein found fewer cases of fever and sepsis in treated children; Dr. Oleske reported some extension of survival.

These studies, though, were small and weren't placebo controlled. (Dr. Oleske, who provides IVIG to AIDS patients at his clinic, unsuccessfully tried to get funding

in 1984 for a larger, follow-up study.)

A placebo—the Latin word for "I shall please"—is a medically inactive substance given to the control group in a drug test. In a randomized trial, where neither doctor nor patient knows who is getting what, a placebo helps to ensure objectivity.

But critics of the NIH study, including many AIDS activists, argue against placebos on ethical grounds. They object to giving a dummy drug to anyone with a fatal illness, particularly to children who can't speak for themselves. To protest the use of placebos in the trial, a New York activist group called ACT UP (AIDS Coalition to Unleash Power) hurled questions and distributed leaflets at a pediatric AIDS conference last month in Newark, N.J.

"We shouldn't use placebo unless there is no reason to believe, none at all, that the treatment group will fare better than the untreated group," says AMFAR's Mrs. Krim. The studies by Drs. Rubenstein and Oleske do suggest there will be a difference, she contends. Furthermore, she says,

WHILE the drug isn't a cure, preliminary studies suggest it could make children more comfortable and perhaps help them to live longer.

historical controls—in this case, knowledge of how untreated children have fared in the past—provide sufficient comparison.

Robert Levine, an ethicist at Yale University Medical School, says he's generally opposed to placebos unless a test drug is scarce—which isn't the case with gamma globulin.

Apart from the objections to placebo use in the study, there are concerns about IVIG itself. For one thing, it isn't totally benign, says Anne Petru, who heads the branch of the NIH trial at Children's Hospital of Oakland, Calif. Dr. Petru says she has witnessed three cases of IVIG-induced anaphylaxis, a rare but overwhelming allergylike reaction that can entail respiratory distress and even death.

For squirming toddlers, the three-hour to four-hour infusions are hard to take. Tiny veins are hard to find. The child's arm must be immobilized on a board to keep the needle in place. In Dr. Oleske's IVIG clinic, children sometimes need sedation or restraints.

Supporters of the test, in which about 100 children are enrolled so far, defend it as pursuit of the greatest good for the

greatest number. "It may be that the most ethical thing to do is to come to a rapid answer so that the most patients benefit from the result," says Keith Krasinski, a doctor at Bellevue Hospital in New York.

The use of the placebo is "very controversial, but it has to be done," adds Dr. Petru of Oakland. "If (IVIG) were \$10 a bottle and 100% safe, all kids would be getting it." (IVIG costs about \$400 for each child's monthly dose.)

As for relying on historical controls, researchers respond that this is imprecise and risks meaningless comparisons. For example, if the past untreated patients were sicker than those currently receiving the drug, improvements attributed to the drug might be an illusion. Another worry is that if a doctor knows his patients are getting the drug, unintentional bias could color the doctor's evaluation.

Researchers suggest, too, that the study can bring even placebo recipients the benefit of regular medical attention. And there is a monitoring board watching for any improvement in the IVIG group, which could eliminate the need to continue the trial.

Mixed Emotions

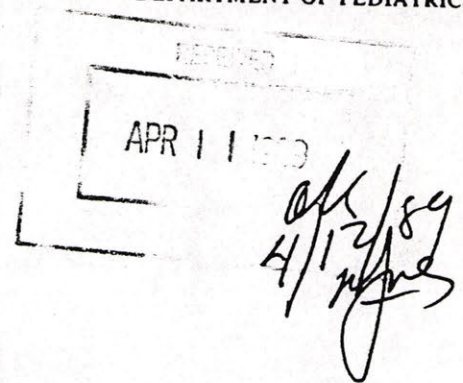
Dr. Oleske himself has watched the trial unfold with mixed emotions. He helped to design the study, but he refused to participate in the tests involving the sickest children because he feels the drug has already been proved effective for them. "We felt comfortable with our experience dating back to 1981," he says. He adds that he isn't able to take part in the other section of the NIH trial, testing IVIG in children who are less sick, because of limited resources and his involvement in a pediatric test of AZT.

The decision to cast a child's fate with a randomized study isn't an easy one for parents to make. Moreover, these parents are often poor, AIDS-infected IV drug users. Even when a child is in foster care, biological parents must be tracked down.

Some parents sign up out of "social-mindedness," says Peggy Weintrub, who heads a branch of the NIH study at the University of California at San Francisco. But "many parents would prefer their kids get the real thing," she adds.

Such was the decision of the Starcross Community of Sonoma County, Calif., a Catholic order that cares for children with AIDS. The order declined Dr. Weintrub's invitation to place one of its children in the trial, opting instead to seek monthly IVIG treatments for the baby girl. "If there was a chance she would benefit, we wanted her to have it," explains Mary Martha Aggeler, a lay sister at Starcross. IVIG, she says, "seems to help them live longer, and that's good enough for me."

Wall Street Journal
5/31/88



April 11, 1989

TO: Committee on Human Research

RE: Protocol entitled "Efficacy of Zidovudine plus Placebo as Compared with Zidovudine plus Intravenous Gammaglobulin in Children with Symptomatic HIV Infection"

I am responding to the Committee's request that the above protocol and consent form be revised. The most substantive question regards the risk:benefit ratio to those HIV infected children who will receive Zidovudine, but will be randomized to receive monthly intravenous albumin infusions rather than intravenous gammaglobulin for 100 weeks.

Clearly, monthly intravenous albumin infusions carry the moderate risk of a time consuming infusion of protein. However, these children will all receive Zidovudine, which is not currently licensed by the FDA for use in patients age 12 and under. The standard of care in our hospital and most others is not to prescribe medication for children if the medication has been evaluated for efficacy and toxicity only in adults. Although toxicity and pharmacokinetics of drugs often differ substantially between children and adults, early studies in children suggest that Zidovudine is safe and effective; definitive Phase II and III studies are now underway but enrollment is closed. At present, the only study in which HIV infected symptomatic children may be enrolled to receive Zidovudine is the one being considered. I believe that a significant benefit to the children we propose to enroll in this study is the controlled receipt of Zidovudine. A second potential benefit is the possibility that the additional evaluation carried out through the protocol may reveal sub-clinical problems which would alter management; an example of this is the use of echocardiography to detect subclinical cardiomyopathy. The benefit to society, although not to the individual patient, of determining the efficacy of Zidovudine plus intravenous gammaglobulin, is stressed in the application.

On the other hand, the risk of monthly intravenous albumin infusions is somewhat diminished if one assumes that all children, regardless of study eligibility, may receive Zidovudine (not a valid assumption). All children receiving Zidovudine will require monthly venipunctures to monitor at least, a CBC with differential; this venipuncture will occur in the proposed study as the intravenous is begun for the placebo or IVIG infusion. An additional venipuncture will not be performed. Finally, if a

SAN FRANCISCO: SCHOOL OF MEDICINE
DEPARTMENT OF PEDIATRICS

child has two or more serious bacterial infections while on study, therapy will be discontinued and intravenous gamma-globulin may then be initiated. The risk for the group at large will be diminished by the careful analysis of data at six month intervals with the discontinuation of the study if intravenous gammaglobulin is efficacious.

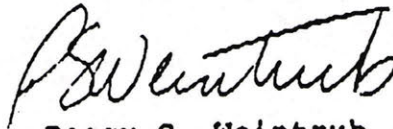
The consent form has been modified to:

- 1) Include Dr. Weintrub's first name,
- 2) Redefine echocardiogram in procedure #9 and risk #4,
- 3) Include the rare risk of skin infection following venipuncture,
- 4) Add the potential "benefit" of the receipt of Zidovudine by all patients.

I appreciate the prompt re-review of this proposal, because I feel that the study has merit and that the use of intravenous gammaglobulin in patients infected with HIV who are receiving Zidovudine must be based on a solid scientific study. A control population not placed at risk, eg. a group followed in parallel who would not receive placebo infusions, would not provide the same data as the one proposed.

Thank you again.

Sincerely,



Peggy S. Weintrub, MD
Assistant Clinical Professor,
Pediatric Immunology/Rheumatology
and Infectious Disease

April 5, 1989

Peggy Weintrub, M.D.
Department of Pediatrics
Box 0105

Re: RETURN FOR FURTHER INFORMATION of "Efficacy of Zidovudine Plus
Placebo as Compared with Zidovudine Plus Intravenous Gammaglobulin in Children
with Symptomatic HIV Infection"

Dear Dr. Weintrub:

During the meeting of March 30, 1989, the Committee on Human Research reviewed your new application. *The members agreed that further information was needed before approval for this application could be reconsidered and asked that you respond to the following points:*

AS seen First, the members were concerned, since there is no benefit to placebo, about having a child randomized to a placebo group for 2 years. The risks will outweigh any benefit to the population. The members referred you to the CHR Guidelines, Appendix G and asked that the study be revised to use a control population which is not placed at any risk. Your response to this issue was requested.

Second, it was requested that, in future applications, the Principal Investigator sign the application.

Third, the following revisions were requested in the consent form:

- 1) Dr. Weintrub's first name should be included in the introductory paragraph of the form.
- 2) It was asked that an Echocardiogram be redefined in Procedure #9 and Risk #4 since it is not an x-ray.
- 3) Risk #1 should be expanded to include rare infections.

Please submit 15 copies of your response and revised consent form to Box 0616. When these have been received, your application will be recirculated to the full committee for further review. *Any unaccepted consent forms in your files should be destroyed to prevent their accidental use.* If you have any questions, please call the office of the Committee on Human Research, 476-1814.

Sincerely,



Reese T. Jones, M.D.
Chairman
Committee on Human Research

EM
Enc.

Source: [REDACTED]

FOR YOUR INFORMATION

June 17, 1989

STATEMENT ON CLINICAL DRUG TRIALS FOR CHILDREN WITH AIDS

UC San Francisco is conducting clinical trials on several experimental drugs to determine whether or not they could be helpful in treating children who have AIDS.

One trial is focusing on the effectiveness of the drug AZT (azidothymidine). All of the children in the study receive AZT, which has been shown to be effective in treating adults with AIDS. The testing will go on for (time?).

UCSF pediatric AIDS specialists are carrying out another study to determine if supplements of immunoglobulin, a blood product carrying antibodies to a variety of diseases, can help fight off the life-threatening bacterial infections that are common to children with AIDS.

In this study all of the children also receive AZT. In addition, half of them receive the immunoglobulin and half receive a "placebo" (a harmless substance used to help researchers determine whether or not the drug being tested is working).

Patients are selected at random by a computer to receive either the drug or the placebo, and neither the doctors nor the patients know who is getting which substance. This is called a "controlled" study, and allows researchers to compare the results of treatment with a certain drug to results of a matched group patients who do not receive the drug. It is the only way for researchers to determine whether an experimental drug works. The results of the treatment will be reviewed at six-month intervals by the National Institutes of Health. And, if it appears to be doing good, a change could be made to give it to all. Conversely, if it appears to do harm it could be discontinued.

The immunoglobulin is given to the children by IV. Contrary to some charges being made, this is not dangerous. The children are not strapped down; ~~Most~~ of are able to walk around and play while they are receiving the IV solution.

The most important reason for doing this particular controlled study is to define the benefit of intravenous immunoglobulin in children with AIDS. There are risks in giving immunoglobulin as well as high costs. The treatment can be as expensive as \$1200 to \$1500 a month and requires that patients receive a monthly intravenous infusion for the rest of their lives. Without proof that the treatment is effective, few patients or physicians would want to continue it. And without a controlled study there is no way to determine the treatment's effectiveness.

List of endorsements for Sat. 17, 1989 action at UCSF. on the use of IV placebos on children with AIDS participating in ACTG 045 and 051 IVIG drug trials:

ACHTENBERG, ROBERTA

ACT UP / NEW YORK

AMARANTO

COALITION FOR IMMIGRANTS AND REFUGEE RIGHTS & SERVICES

EL GRIECO, HELEN from N.O.W.

GONZALEZ, JOE from MISSION MENTAL HEALTH CENTER

HARVEY MILK DEMOCRATIC CLUB

INSTITUTO FAMILIAR DE LA RAZA

LATINO AIDS COALITION AND CHRIS SANDOVAL

LATINO AIDS PROJECT

LESBIAN UPRISING

MANO - A - MANO

MAN WHO CARE ABOUT WOMEN'S LIVES

MOORE, BRANDY from BLACK COALITION ON AIDS / ASSISTANT TO WILLY BROWN

PROJECT INFORM AND MARTIN DELANEY

P.W.A. SF

ROFES, ERIC from SHANTI

STAR CROSS MONASTERY

S.F. AIDS FOUNDATION AND PAT CHRISTIEN

THIRD WORLD AIDS ADVISORY TASK FORCE AND HANK TAVERA

KAISER PATIENT ADVOCACY UNION

ACT UP SAN FRANCISCO

AIDS COALITION TO UNLEASH POWER
2300 Market Street # 68 San Francisco, CA 94114

Events Line (415) 563-0724

10
Richard E. Puglia

May 31, 1989

Office on Human Research
Box 0616
San Francisco, CA 94143

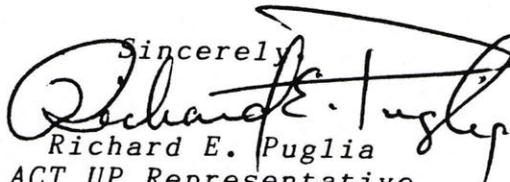
Attn: Mr. Reese Jones,
Chairman

Dear Mr. Reese:

Enclosed is a copy of our proposed demonstration on June 17th against the use of placebos on infants and children with AIDS, i.e. ACTG 051 and ACTG 045.

ACT UP S.F. would like to schedule a meeting with you and the entire Institutional Review Board as soon as possible or preferably no later than June 15th.

We look forward to an expedient response in this matter and to a productive meeting.

Sincerely,

Richard E. Puglia
ACT UP Representative

REP
Encl.

In his book, MORNING GLORY BABIES: CHILDREN WITH AIDS AND THE CELEBRATION OF LIFE, Brother Toby of Starcross Community relates how:

Some researchers wanted to have us put Melissa in a controlled study, a kind of medical lottery. There would be a 50 percent chance that she would receive the gamma globulin. We did not dispute the scientific value of the study, but we did not care for the odds.

Because of ill health he is unable to be here, so he sent this message for today's gathering:

It is ethically indefensible to withhold from a child any treatment which is known not to be harmful and is likely to improve the quality of her or his existence. The politics of research must never be allowed to deprive a child of a single hour of happiness.



Who wrote this

IVIG Drug Trials in Children with AIDS Raise Serious Ethical Concerns

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Background

The National Institute of Allergy and Infectious Diseases (NIAID) is currently conducting two clinical trials in pediatric AIDS patients to evaluate the effectiveness of intravenous immunoglobulin (IVIG) against bacterial infections in children with HIV disease.

In one study, children are given AZT and IVIG or AZT and IV albumin placebo. In the second study, children are given IVIG or IV albumin placebo.

In both studies, IVIG (or the albumin placebo) is administered once a month. The intravenous infusion takes approximately four hours. Both studies will continue for a two year period.

Analysis

Studies of this nature, involving pediatric AIDS cases and the use of IV placebos, raise serious ethical concerns which must be addressed more fully before these trials are allowed to continue.

The San Francisco AIDS Foundation is deeply concerned that the current protocol (study design) for both of these trials does not clearly delineate the end point of participation in the trial for a given child. For example, if the health of a child in the study begins to deteriorate, at what point is the study code broken to determine if the child is receiving a placebo or IG? Is the child allowed to die or are specific immune system markers used to determine the level of disease progression in the child? Do all participating physicians and the parents/guardians of the children fully understand what the end points are?

The administration of a placebo via intravenous infusion is also of concern. Can this be justified when these young children must endure this invasive procedure over a four-hour period every month? Are other alternatives available? There are clear risks to the health of an

immune suppressed child presented by intravenous infusions. Are these risks acceptable?

There is also historical data available that indicates IVIG is useful in fighting bacterial infections in other immune suppressed children. Given that information, is the IV administration of a placebo justified or warranted in either of these trials?

Finally, what process has been developed to ensure that the parent/guardian of the child has complete understanding of the implications of the protocol prior to enrolling the child in the study? Is a consistent process used by all participating research units? How is this monitored?

Until these questions receive thoughtful consideration and are openly discussed and resolved by the Investigational Review Boards of the participating institutions, in conjunction with concerned community AIDS activists, the use of placebos in these particular trials should be suspended.

This does not mean that all trials utilizing placebos are unethical. On the contrary, an intelligent analysis of these trials provides a framework for the appropriate use of placebos. For the sake of these children, their parents and the attending physicians, these questions must be addressed in full now, rather than later.

CONFIDENTIAL

SAN FRANCISCO: OFFICE OF PUBLIC SERVICE PROGRAMS

Handwritten initials "MB" and "BMB" next to a circle containing the handwritten text "cc MR".

June 12, 1989

Memo To: TOM GWYN
BARBARA ATKINSON

From: MEREDITH MICHAELS

Subject: ACT UP!

Attached is some additional information from ACT UP regarding the clinical trials involving infants who have AIDS.

Second, members of the gay community have told me that ACT UP plans to put pressure on the UC Board of Regents with respect to Compound Q. Specifically, they will be asking the Regents to provide them with:

1. A timetable for clinical trials (and accountability). Certain ACT UP members believe that Volberding is purposefully, but unnecessarily, expanding the time needed to conduct the trials.
2. Written pricing policies.
3. The opportunity to review the research protocol(s).
4. Recruitment procedures for Phase II clinical trials.
5. A determination as to whether there will be an inpatient requirement which could hold up the testing.

ACT UP will officially request this information as well as an opportunity to be on the agenda for both the June 15/16 Regents meeting in Los Angeles and the July 20/21 meeting in San Francisco.

I'll keep you posted if I hear anything else.

WW III BABIES

In every world war infants die in great numbers. So too is the case in the current war against AIDS. You can find many infants abandoned behind crib bars in hospitals at a cost of \$70,000 per year. Due to the present state and federal policies, many of these babies live and die in their cribs buried by red tape. Some don't learn how to walk until they are three years of age because there is no one with the time to teach them to do so. There are too few nurses for the task, hospitals being severely understaffed. Throughout the 1980's and to date children around the country are being denied the right to attend public schools without putting up a fight for their rights. One such family in Florida had their house burned to the ground because the parents of two children with AIDS refused to cave in to public pressure, and continued to have their children attend school.

In San Francisco, a child with AIDS was denied the right to bathe in a physical therapy pool due in part to the misinformation given by Dr. Lorraine Day.

Unfortunately, only recently has the issue of children with AIDS come into the national focus since they are no longer a silent minority, nor will the statistics continue to go unnoticed.

Nationwide statistics from the Center of Disease Control, as of Feb. 6 1989, are as follows:

	<u># CASES</u>	<u># DEATHS</u>
Hemophiliacs	84	44
High risk parents	1,087	591
Transfusion recipient	175	105
Undetermined	54	28
Unreported	?	?
Totals	1,400 or more	768 or more

* 76% of these children are minorities.

The total number of cases by May 1989 is 1,708, and it is estimated that 17,000 children are HIV+

In 1987 a senate select committee estimated that there were 100 HIV+ infants to every one infant with full blown AIDS. However, today it is believed that there is a 50% chance that the infant can shed the virus and remain seronegative. By 1991 pediatric experts predict that there may be as many as 20,000 children affected by AIDS. People who still think AIDS is a gay disease, may be surprised to know that 30% of all cases being reported now are heterosexual, either adults or children. Only between 10% to 20% of these children may grow up to be gay & lesbian adults if God stops picking his/her favorite flowers. God save Roe vs. Wade!

The following is a list of organizations helping children with AIDS in the bay area:

- The Center in Oakland offers individual counseling and financial assistance. They also sponsor fundraisers such as the upcoming Children for Humanity Programs, headed by Meryl Collins,

Creative Director. A choir of children will sing for children with AIDS. The event will take place at the All Saints Cathedral in Hayward on May 28th from 9:00 am to 1:00 pm. All donations will go to the Children helping children fund at the Center headed by brother Kevin Worth.

- Star Cross Monastery in Sonoma county is a hospice home for children with AIDS. They have recently bought another house in Santa Rosa to provide support to families who have adopted babies with AIDS. The support consists of baby sitting, transportation co-Ops and grief counseling. The Star Cross family also wish to start a support group for women with AIDS or at risk if they have not done so already. They are also working on drafting legislation for children with AIDS to improve the current placement policies in effect.

- The Children's Quilt Project is making Quilts to bring attention to the plight of children with AIDS, as well as to offer creative outreach services such as toy & clothing drives, volunteers for individual care and collect and dispense information to the public. They also hope to provide financial assistance in the near future, given that more grants become available. Perhaps the up coming concert against AIDS will be of substantial assistance to some of these organizations.

- Aid to Adoption of Special Kids (A.A.S.K.) assists in the adoption and placement of children with AIDS to heterosexual, gay and lesbian couples who qualify. They too are working on drafting a new legislative policy fundamental to freeing all children for adoption.

- Jewish Family/Children Service AIDS Project offers emergency services i.e. financial assistance and counseling to parents and guardians.

- The Federal Government offers financial assistance through the Social Security Administration, but it is unknown to this writer at this time as to who pays the hospital expenses of abandoned children.

- California Children's Services defrays the cost of blood services for hemophiliac children with AIDS.

- The Hemophiliac Council of California (H.C.C.) is a co-sponsor with Stanford Children's Hospital for a week long stay at Camp Cazadero. Dan Francis from H.C.C. also counsels "The night of the living bleeders" named by and for hemophiliac teenagers, some of whom have AIDS.

- Act Up San Francisco, P.W.A's S.F. and the Children's Quilt Project do an annual toy drive during the holidays for children with AIDS under 13 years of age. Act Up S.F. is also presently working on treatment issues for people and children with AIDS by drafting a 6 point legislative proposal for congress women Nancy Pelosi and Barbara Boxer.

- The Warwick Foundation founded by Dionne Warwick recently created a model comprehensive pediatric AIDS program, which will be unveiled in New York city this June. This program will later be replicated in the other nineteen cities in this country that have the highest incidence of AIDS.

- Face to Face in Sonoma county offers counseling and financial aid if funds are available.

- Act Up Sonoma is working on treatment issues and recently supported more funding for the organization mentioned above.

- Shanti is offering help with housing for women and children with AIDS.

- The AIDS Emergency Fund gives financial assistance to the parents or guardians of children with AIDS.

- The Center of Attitudinal Healing in Marin county offers group emotional support.

- Catholic Charities sometimes gives financial assistance if funds are available.

Children's Hospital in Oakland has a pediatrics ward for children with AIDS. Along with U.C.S.F. and Moffitt at U.C.S.F. all three hospitals are presently conducting Intravenous Immunoglobulin (I.V.I.G.) double blind placebo controlled studies on symptomatic AIDS and ARC children from 1 month old to 12 years old. They all have a T4 cell count of 600 or less. Hemophiliacs are excluded from the studies. Phase II and III for these studies began on May 12th 1989 for 366 patients. So far there are only 40 patients enrolled.

The National Institutes of Health (NIH), which oversees the Federal ACTG (AIDS Clinical Trials Group) seems to have finally realized that it is impossible to enroll large numbers of HIV infected people in trials using placebos (inactive substances against which test drugs are sometimes measured) because such trials require many people who are ill to receive no treatment. Many who do enroll in such trials quite understandably continue taking drugs outside the trial and thus skew trial results. This realization has not diminished the passion of the NIH for employing placebos in trials for HIV infected children who cannot speak out for themselves and lack enough vocal advocates: the new batch of NIH AIDS trials has no fewer than three placebo controlled trials.

Until May 1988 children with AIDS have been almost wholly excluded from drug trials and therefore, from experimental treatment including AZT. The government listed TRIALSA has fewer than 4 trials for children with AIDS in the Bay area. It is ironic indeed that the only such trial, which is not small and preliminary, is a placebo controlled study. As stated above, one that is dangerous to its subjects. Please note that because their immunity systems are still developing, children under the age of 2 years have a shorter life expectancy than do women and

then men.

Since 1980, Dr. Ayre Rubenstein, a NYC Pediatrics Professor, has treated immuno-deficient children with intravenous immuno-globulin (I.V.I.G.), a blood derivative. Dr. Rubenstein reported that over 2 years, only 7% of IVIG treated children developed bacterial infections, while 78% of those untreated developed them.

Other doctors questioned those results. A national trial was designed and \$ 3.8 million was allocated for double-blinded, placebo controlled studies. For many children with AIDS, whose parents are most often people of color, poor, IV drug users and HIV infected themselves, participating in a drug trial offers the best chance of receiving quality treatment. Babies have no chance of giving informed consent and the prospect of better care for children may be an un-planned coercion of their parents or guardians.

The IVIG trial of children with AIDS exposes them to IV-induced infections. Any IV administration carries the risk of infection. While taking a promising drug IV can be justified, there is no excuse for using IV placebo in immune suppressed persons.

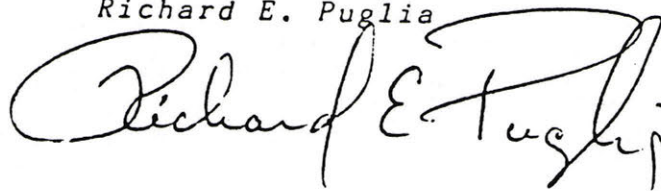
The National Cancer Institute (N.C.I.), directed by Dr. Samuel Broder, wanted to begin testing DDI in infants with AIDS because there are no approved treatments for them, and AZT appears to be highly toxic in infants. However, the FDA was unwilling to permit testing in infants until a toxic dose was established in adults.

DDI (Dideoxyinosine) a promising nucleoside analogue, reverse transcriptase inhibitor and a less toxic derivative of DDA has been found to be about half as active against HIV as AZT, but 100 times less toxic. This ACTG064 study is now on the ninth dose escalation level in Phase I trials at NYU and has so far failed to establish significant toxicity in adults.

Last January, Bruce Chabner, head of the Cancer Division at N.C.I. testified before the FDA, many months after the DDI trials began, with early encouraging results of increased weight and energy in adult subjects. The N.C.I. further went on to criticize the FDA for not allowing the testing of DDI on infants with AIDS with the promising data on record. Shortly there after, the N.C.I. was given the go ahead. Four months have since passed and the Phase I and II studies on infants with AIDS is looking real good according to Dr. Phil Pizzo, who supervises the studies. Twenty children are involved in two groups. One is for children who have been on previous antiviral treatments and who are symptomatic. And the other group is for symptomatic children who were not on other antiviral treatments. Both groups are free of placebos, and preliminary results are due this mid summer and then again in September at the ICAAC Infectious Disease meeting to take place in Houston, Texas. More results from adult studies are expected in Montreal this June. ACTG091 is another study opening up to 25 children with AIDS at the University of Miami in a matter of weeks, and will be supervised by Dr. Scott.

It is written in our Constitution that all americans have the right to petition government with their grievances. Perhaps if more americans excised that right with activism, they can move a slow bureaucracy with fresh new ideas. Perhaps we can write to Barbara Bush and Princess Diane and ask them to stop writing form letters and to review the legislative proposals and programs drafted for children with AIDS by the organizations already stated in this article. Perhaps we can call or write letters to our congressional representatives and ask them to push for more research staff in the FDA or to amend testing and approval mechanisms for flexibility in times of crises. Perhaps we can write some more to the National Institute of Health and local hospitals, asking them to allow PWA's to have a say in drafting drug protocols. Perhaps we can visit the World Health Organization and tell them to pressure governments to allow the use of drugs tested and proved reasonably safe to be released to any patient with a terminal illness. "Compassion will not cure AIDS alone" but allowing one the freedom to choose a reasonably safe drug when all else fails is an act of compassion in itself. Perhaps we can demand that the Congress of these United States to declare war on AIDS and to take all positive action now. Or perhaps we can sit back and hope for expanded Phase II trials of DDI and GLQ223, or we can hope for something else down the pipeline and sit back, say we're too busy, too busy arguing about what is politically correct, too busy watching T.V. counting the numbers of how many died and too busy to remember.

Richard E. Puglia

A handwritten signature in cursive script, reading "Richard E. Puglia". The signature is fluid and stylized, with a large, sweeping initial "R".

Proposed Procedures for ACT UP Demonstration

Friday

News handles press inquiries with Diane Wara

Saturday
9 am

Designated group meets in L-191 (between Haas Pavilion and Langley Porter).

Hold L-191 for any press who might show up.

_____ to talk to press after meeting in L-192.

Saturday
Noon

Outside -- Bruce W. Spaulding, police, news people.

Inside -- (room _____) Paul Volberding and Diane Wara wait for interview requests. News people to bring press in one by one or all together for interviews.

NOTE - police needed to stand by in north-south corridors into Moffitt Long and east-west corridors into Moffitt lobby to prevent press or demonstrators from gathering. Also protect both elevators into hospital.

News Inquiries - locate Carol Fox and she will handle any situation.

Beeper # 739-1035.

Alice Trinkl on call for weekend. Call 476-2557 or beeper #739-1034.

Weekend media requests -- Paul Volberding and Diane Wara available for comments to press.

TO: Peggy Weintrub, M.D.
Box 0105

RE: Efficacy of Zidovudine plus Placebo as Compared with Zidovudine plus
Intravenous Gammaglobulin in Children with Symptomatic HIV Infection

The UCSF Committee on Human Research (an Institutional Review Board holding Department of Health and Human Services assurance #M-1169) has approved the above request to involve humans as research subjects.

APPROVAL NUMBER: H1267-04357-01. This number is a UCSF CHR number which should be used on all consent forms, correspondence and patient charts.

APPROVAL DATE: April 12, 1989. Full Committee Review

EXPIRATION DATE: April 12, 1990. If the project is to continue, it must be renewed by the expiration date. See reverse side for details.

ADVERSE REACTIONS/COMPLICATIONS: All problems having to do with subject safety must be reported to the CHR within ten working days.

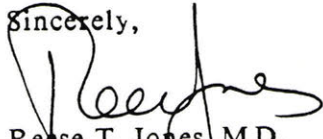
MODIFICATIONS: All protocol changes involving subjects must have prior CHR approval.

LEGAL NOTICE: The University will defend and indemnify a principal investigator in legal actions arising from research activities involving humans only if the activities had current CHR approval.

QUESTIONS: Please contact the office of the Committee on Human Research at (415) 476-1814 or campus mail stop, Box 0616.

Good luck on your project.

Sincerely,



Reese T. Jones, M.D.
Chairman
Committee on Human Research

cc: Drug Information and Analysis Service

HEPC Project # 89004357

**Memorandum**

Date October 25, 1988 *KEEP protocols by book*
From Beverly Bond, R.N., B.S., CCRN, Protocol Specialist
Subject Amendments to Protocol ACTG #051
To Protocol ACTG #051 Team Members

* Protocol ACTG #051 has been approved by the FDA. However, several Drug Company concerns prompted changes which now require a formal amendment. The major change involves the allowance of prophylaxis treatment for children who have had a previous episode of laboratory documented Pneumocystis carinii (PCP) or develop a laboratory documented episode of PCP while on study.

Changes have been made in **boldface** type for ease of identification. Changes are as follows:

SCHEMA - The Schema has been adjusted to include "**Current Prophylaxis with Trimethoprim/Sulfamethoxazole (TMP/SMX)**" under the "stratify" section.

Section 6.141 - A sentence has been deleted from this section:

"In addition, a child with two or more episodes of recurrent herpes zoster infection or chronic zoster defined as > 30 days' duration regardless of therapy, will be considered as AIDS-defining for the purpose of this protocol."

This sentence will not significantly effect the patient's entrance into the protocol. Also the CDC definition of AIDS will be used when AIDS is referenced.

Section 6.1512 - Refer to the heading of "***Lymphadenopathy**"; under "Note"; this section has been revised to read:

"Note: If this is the only **minor** finding, the child must have at least 1 of the first 2 major findings above."

Section 6.16 has been changed to read:

"Absence of acute opportunistic infection at time of entry. Children receiving maintenance therapy, including amphotericin B for fungal disease or INH/rifampin for specific tuberculosis treatment, will be eligible."

Section 6.17 has been added to the protocol:

"Children receiving prophylaxis treatment for a previous episode of laboratory documented Pneumocystis carinii pneumonia (PCP) may remain on such therapy and will be eligible for inclusion in this protocol. However, patients receiving trimethoprim/sulfamethoxazole (TMP/SMX) for PCP prophylaxis will follow the TMP/SMX regimen as outlined in section 7.43."

Sections 6.18 and 6.19 have been renumbered accordingly.

Section 6.25 has been added to the protocol:

"Children with known hypersensitivity to immunoglobulin."

Sections 6.26 through 6.296 have been renumbered accordingly.

Section 6.27 (previously section 6.26) has been changed to read:

"Children receiving antibacterial prophylaxis for otitis, sinusitis, or urinary tract infection. Children receiving prophylaxis treatment for PCP prior to the first episode of laboratory documented PCP, will discontinue treatment."

Section 6.296 has been changed to read:

*
"Platelet count < 75,000/mm³ (except for HIV associated thrombocytopenia for which thrombocytopenia will not be an exclusion)."

Section 6.30 has been added to the protocol:

"Children with active HIV thrombocytopenia whose Investigator believes IVIG therapy is required."

Sections 6.31 and 6.32 have been renumbered accordingly.

Section 7.42 has been revised to state:

"The use of antibacterial agents for bacterial infections such as otitis media is prohibited. Prophylaxis for Pneumocystis carinii pneumonia (PCP) in children who have not had a previous laboratory documented episode is prohibited. However, children who have had or develop a laboratory documented episode of PCP, may receive trimethoprim/sulfamethoxazole (TMP/SMX) or an alternative

treatment for continuous PCP prophylaxis. Patients receiving TMP/SMX for PCP prophylaxis will follow the TMP/SMX regimen as outlined in section 7.43. TMP/SMX treatment will be limited to three days a week."

Section 7.43 has been added to the protocol:

"A regimen of TMP, 75 mg/m² per dose given BID, 3 times a week (MWF schedule) and SMX, 375 mg/m² per dose given BID, 3 times a week (MWF schedule) is recommended. Children who are allergic or cannot tolerate TMP/SMX treatment may receive alternative therapy. Children must be monitored closely for possible toxicity due to combination therapy with zidovudine."

Sections 7.44 and 7.45 have been renumbered accordingly.

Section 8.1, "Dose Modification for Hematologic Toxicity and Progressive Bone Marrow Suppression", and Section 8.2, "Dose Modification for Non-hematologic Toxicities", have been restructured for easier reference. Content of these two sections basically remains the same as the ACTG #051 protocol dated 8/25/88 and labeled Version 1.0. A specific change that has been made is marked by an asterisk. This asterisk has been placed to reference the 25,000-74999/mm³ platelet parameter located under the definition chart in Section 8.1. This reference states:

"*Patients with documented immune thrombocytopenic purpura (ITP) are excluded from zidovudine dose reduction for documented isolated thrombocytopenia."

Sections 8.12 and 8.22 have been added to the protocol in order to address the possibility of toxicity when prophylaxis therapy is administered along with the study drugs. These sections now state:

"Children receiving prophylactic therapy for a laboratory documented episode of PCP while on study, must be monitored closely for possible toxicity due to combination therapy with zidovudine. If toxicity develops and zidovudine dose reduction is required, the prophylactic therapy will be temporarily discontinued. Prophylactic therapy will be resumed when the child's lab values stabilize on the reduced zidovudine dose."

A third stratification has been added. Section 10.1 has been revised to read:

"(1) history of one or more serious bacterial infections within two years prior to entry, defined as: meningitis, bacteremia, pneumonia, osteomyelitis, septic arthritis, acute mastoiditis, acute sinusitis, and abscess of an internal organ, (2) prior zidovudine therapy, and (3) current prophylaxis with trimethoprim/sulfamethoxazole (TMP/SMX)."

ACTG 051

A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO
EVALUATE INTRAVENOUS GAMMA GLOBULIN IN CHILDREN WITH
SYMPTOMATIC HIV INFECTION RECEIVING ZIDOVUDINE

A Multicenter Trial of the AIDS Clinical Trials Group

Sponsored by:

The National Institute of Allergy
and Infectious Diseases

Pharmaceutical Sponsors:

Cutter Biological
Burroughs-Wellcome Company

Study Chairman:

Stephen A. Spector, M.D.
University of California, San Diego
and the ACTG Pediatric Committee

NIH Coordinators:

Contact Person - James F. Balsley, M.D., Ph.D., Medical Officer, AIDS
Program, NIAID

Judith Feinberg, M.D., Group Leader, Medical Officer, AIDS Program, NIAID

Anne Willoughby, M.D., National Institute of Child Health and Human
Development

Protocol Specialist: Beverly Bond R.N., B.S., CCRN

FINAL PROTOCOL

Version 2.0
10/24/88

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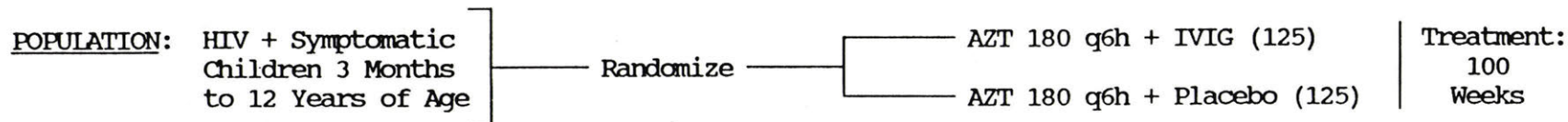
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NIAID ACTG/PROTOCOL 051

PHASE III AZT/IVIG IN SYMPTOMATIC HIV INFECTED CHILDREN

DESIGN: Multicenter Double Blind, Placebo Controlled Out-patient Study



Stratify:

- One or More Serious Bacterial Infections Within 2 Years
- Prior AZT Therapy
- Current Prophylaxis with Trimethoprim/Sulfamethoxazole (TMP/SMX)

ENDPOINTS:

Primary -Reduction in Frequency of Serious Bacterial Infections

Secondary

- Prolongation of Survival
- Comparative Tolerance of the Two Regimens
- Progression to AIDS for Patients Entering with ARC
- Changes in Clinical, Immunologic and Virologic Outcomes

STUDY CHAIR: S. Spector

1.0 INTRODUCTION

The acquired immunodeficiency syndrome (AIDS) was first described in the United States in 1981. The illness is characterized by a cellular immune deficiency predominantly affecting T-helper cell function which makes the individual susceptible to opportunistic infection and certain malignancies. AIDS was originally described in adult male homosexuals but has also affected a number of other groups including hemophiliacs, intravenous drug abusers, sexual partners of AIDS patients, and children. Transmission occurs through one or more of four routes: sexual contact, administration of blood or blood products, intravenous drug administration using contaminated needles and passage from an infected mother to her child.

The etiologic agent of AIDS is thought to be a new retrovirus referred to as the human immunodeficiency virus (HIV). HIV infection results in a spectrum of clinical manifestations ranging from asymptomatic seropositivity to marked immunologic dysfunction. Clinical manifestations include symptoms such as dementia/encephalopathy and severe weight loss as well as opportunistic infections and unusual malignancies.

As of September 1987, the Centers for Disease Control had received reports of 41,770 adult/adolescent cases of AIDS in the U.S. In addition, 584 pediatric cases (children < 13 years of age) have been reported. In 78% of the pediatric cases, HIV infection was acquired through perinatal transmission; 12% of the diagnosed children received HIV-infected blood/blood products and 5% were children with hemophilia who received contaminated coagulation factors. In 4% of the children, the route of HIV transmission is unknown (1).

The clinical presentation of HIV infection in children, whether acquired through perinatal transmission or from blood/blood products, is variable. The Centers for Disease Control recently revised the case definition for AIDS (August 1987, see Appendix I). The current definition now recognizes the variety of syndromes associated with pediatric HIV infection such as neurologic manifestations and lymphoproliferative disease (2). In comparison to adults infected with HIV, children are more likely to be symptomatic throughout the course of their infection. It has been estimated that by 1991, there may be 10,000 to 20,000 symptomatic HIV-infected children in the U.S. (3).

Among 575 children with AIDS reported to the Center for Disease Control, 60% of the children died within 1 year of their diagnosis. Mortality was not dependent on route of HIV acquisition. However, children presenting with lymphocytic interstitial pneumonitis had an approximate 30% mortality rate at 1 year from diagnosis while children who presented with Pneumocystis carinii pneumonia (PCP) or esophageal candidiasis had a 70% mortality rate at 1 year from diagnosis. Age at the time of AIDS diagnosis was also a variable which affected the

observed mortality rate. Children who were < 1 year of age at diagnosis and children who were > 1 year of age at diagnosis had approximate 1 year mortality rates of 70% and 50%, respectively (4).

Thus, HIV infection in the pediatric population is most often associated with symptomatic disease and poor prognosis. Intervention with antiviral therapy may be effective in altering the course of disease and decreasing mortality in this population.

Zidovudine (3'-azido-3'-deoxythymidine; azidothymidine; AZT; BW 509U; Retrovir), a potent in vitro inhibitor of the replication of HIV, has been shown to decrease the mortality and the frequency of opportunistic infections in certain adult patients with symptomatic HIV infection (5). It is therefore likely that symptomatic HIV-infected children may also benefit from specific antiviral therapy. Phase I studies in children 3 months to 12 years of age have evaluated the safety and pharmacokinetics of zidovudine in this population. These studies have indicated that zidovudine can be administered to children in doses which can be tolerated and which will achieve presumed therapeutic plasma and cerebrospinal fluid drug levels (6,7,8).

Children with HIV infection have unusually high rates of bacterial infections, which are typically severe and often recurrent (9,10). Like HIV-infected adults, HIV-infected children may have both profound cellular and humoral immunodeficiency (11,12). Adults, however, do not typically have major problems with recurrent bacterial infections. This difference between HIV-infected adults and children may be due to infants' relative immunologic immaturity and antigenic naivete which, coupled with B-cell dysfunction, leads to an inability to respond to bacterial challenge.

Bacterial infections are now recognized to be a frequent finding in HIV-infected children. In a retrospective review of 46 children with symptomatic HIV infection, Bernstein et al described 26 patients with at least one episode of serious bacterial infection; there were 27 episodes of sepsis in 21 patients (13). The clinical syndromes most often appreciated included: sepsis, pneumonia, skin and soft tissue infections, and meningitis. Streptococcus pneumoniae and Salmonella species were the most common isolates.

In a retrospective review of 70 HIV-infected patients, Krasinski et al found that 44 had had at least one positive bacterial culture and that 30 had well-documented bacterial infections (14). There were 1,163 cultures performed on these 44 patients: mean = 26.5, median = 15, range 1-132. There were 132 documented episodes of bacterial infection in 30 patients: mean = 4, median = 3, range 1-11. The most common clinical syndromes identified included: pneumonia 24/132 (18%), urinary tract infections 24/132 (18%), skin and soft tissue infection 18/132 (14%), and primary 17/132 (13%) and secondary 14/132 (11%) bacteremias. The most common isolates recovered were E. coli

31/183 (17%), S. epidermidis 26/183 (13%), S. viridans 18/183 (10%), S. aureus 15/183 (8%), S. pneumoniae 14/183 (8%), and S. fecalis 13/183 (7%). However, taken together, Enterobacteriaceae accounted for 60/183 (33%) of isolates and were represented by Klebsiella, Proteus, and Morganella. Pseudomonas aeruginosa and other Pseudomonas species represented 15/183 (8%) of isolates. The case-fatality ratio in this overall group of patients was 18/70 (26%), but was 17/30 (56%) for patients with documented bacterial infections. Bacterial infections contributed to the death of 4 of the patients, but direct causality could not be ascribed to bacterial infection alone for any death.

Because pooled human serum immunoglobulin is effective in reducing the rate of bacterial infection in patients with congenital defects of humoral immunity, particularly those with agammaglobulinemia (15), theoretically it should reduce the rate of bacterial infection in HIV-infected children as well.

This randomized study proposes to evaluate the safety, tolerance and efficacy of zidovudine plus IVIG versus zidovudine plus placebo administered for a 100-week period. The mortality, rate of serious, life-threatening bacterial infections and opportunistic diseases will be compared between the two treatment groups. Because of the marked difference in mortality between children who present with opportunistic infections versus children with lymphocytic interstitial pneumonitis (LIP), children with LIP as their only clinical manifestation of HIV infection will be excluded from enrollment in this study.

2.0 BACKGROUND

2.1 Zidovudine

2.11 Pharmacokinetics

The pharmacokinetics and bioavailability of zidovudine were evaluated during a Phase I trial in adult AIDS and ARC patients. In addition, two Phase I pharmacokinetic studies have been initiated in children 3 months to 12 years of age with symptomatic HIV infection. Preliminary analysis of the pharmacokinetic data from these studies indicate that, in general, the pharmacokinetics of zidovudine in children (5 months to 12 years of age) is similar to the pharmacokinetics in adult patients.

Following a one-hour intravenous infusion of zidovudine, at a dose of 80 mg/m², the mean terminal half-life (t_{1/2}) in 12 children was 1.57 hours (range: 0.73 to 2.52 hours). There appeared to be a trend towards higher clearances in the younger patients (ages 2 to 3 years). However, the

number of patients (four) in this age range was small and the trend needs to be validated in additional children. The mean zidovudine plasma level (N=9) at the end of infusion (1 hour) and 6 hours post dose (80 mg/m^2) were 1.74 ug/ml and 0.09 ug/ml , respectively. Total urinary recovery averaged 86% with zidovudine accounting for 24% and GAZT contributing to 62% of the recovery.

Following oral dosing of 80 to 120 mg/m^2 , peak zidovudine concentrations ranged from 1.1 to 1.4 ug/ml . Peak levels generally occurred at 0.5 hours post dose. Bioavailability estimates ranged from 0.71 to 1.0 indicating adequate oral absorption. Simultaneous plasma and spinal fluid samples were obtained following intravenous and oral zidovudine dosing. The samples were collected between 2 to 5 hours post-dosing. The mean CSF/plasma ratio for 7 patients who received intermittent zidovudine (every 6 hours) was 0.69. The mean CSF/plasma ratio for 8 patients receiving zidovudine by continuous intravenous infusion was 0.28. The overall mean CSF/plasma ratio for all 15 patients evaluated was 0.47. This is a similar ratio to that determined in adult patients and is considered a favorable parameter in light of the extensive HIV neurologic disease observed in pediatric patients.

2.2 Pediatric Phase 1 Clinical Data

Two phase 1 studies have been conducted to determine the safety, tolerance and pharmacokinetic of zidovudine in the HIV-infected pediatric population. Children 3 months to 12 years of age with symptomatic HIV infection (CDC classification: Class P-2), are enrolled in the studies. One study evaluated the safety and pharmacokinetics of intermittent intravenous infusion of zidovudine followed by chronic oral dosing. The second study evaluated the safety and pharmacokinetics of continuous intravenous infusion.

2.21 Phase 1 Intermittent IV/PO Study

Children were enrolled into one of three dose groups and received 4 to 8 weeks of intravenous dosing followed by chronic oral therapy. The oral dose administered is 1.5 times the intravenous dose. The following regimens have been evaluated:

<u>Intravenous</u>	<u>Oral</u>
$80 \text{ mg/m}^2 \text{ q } 6 \text{ hr.}$	$120 \text{ mg/m}^2 \text{ q } 6 \text{ hr.}$
$120 \text{ mg/m}^2 \text{ q } 6 \text{ hr.}$	$180 \text{ mg/m}^2 \text{ q } 6 \text{ hr.}$
$160 \text{ mg/m}^2 \text{ q } 6 \text{ hr.}$	$240 \text{ mg/m}^2 \text{ q } 6 \text{ hr.}$

Sterile solution for injection has been administered by mouth. A liquid formulation is not yet available that will provide appropriate oral doses for children. In most cases, intravenous therapy has been administered via a central venous catheter. Several children who received the intravenous drug by peripheral vein access developed phlebitis at the catheter site.

Thirty-six children with Class P-2 HIV infection, according to the CDC classification system, have been enrolled into the study. HIV infection was acquired perinatally in 19 cases, by transfusion of blood products in 16 cases (7 hemophiliacs) and by unknown route of transmission in 1 case. Their ages range from 5 months to 13 years. The current patients have been enrolled in the study for one to sixteen months. Eighteen of the thirty-six patients were enrolled into the first dose group (80 mg/m² IV); thirteen children have been enrolled into the second dose group (120 mg/m² IV) and five children have been entered into the third group (160 mg/m² IV).

Thirteen of the thirty-six children have required dose modification due to the onset of hematologic abnormalities. Eight of the 13 children had their dose reduced by 15 to 30 percent for anemia (4), neutropenia (2), and anemia/neutropenia (2). In all cases, zidovudine dosing was returned to the original dose level after stabilization of hematologic parameters. Stabilization generally occurred by 4 weeks after dose reduction. Six of the 13 children, including one with a previous dose reduction, had their therapy temporarily discontinued and restarted at the same or at a reduced dose level. Dosing was generally interrupted for a period of ≤ 7 days. Zidovudine was temporarily discontinued for the following: anemia (1), neutropenia (4), and pancytopenia (1). Five children have received one or more transfusions for a decrease in hemoglobin. However, two of these children were transfusion dependent prior to study entry.

Two patients were permanently discontinued from this study and enrolled into the continuous intravenous infusion study in an attempt to interrupt progression of HIV-related symptoms.

Two patients have developed an opportunistic infection while participating in the study. One child developed *Pneumocystis carinii* pneumonia diagnosed clinically 4 months after enrollment in the trial. He was successfully treated with TMP/SMX. Zidovudine dosing was continued during TMP/SMX therapy. The second child developed disseminated varicella 3 months after enrollment. She was

successfully treated with IV acyclovir while on zidovudine. Four children have developed one or more serious bacterial infections. These included bacteremia and pneumonia with pathogens such as *Pseudomonas*, pneumococcus and *Streptococcus*. Minor infections such as otitis media and sinusitis have been reported in approximately one-third of the participants. In addition, a number of children developed phlebitis or cellulitis at the peripheral vein catheter site. In some instances, this resulted in an associated bacteremia.

A 2-year old female with HIV infection characterized by recurrent bacterial infections, failure to thrive, lymphadenopathy, encephalopathy, leukocytosis and chronic microcytic anemia developed an S₃ gallop and a change in left ventricular contractility on echocardiogram 4 weeks after enrollment in the study. She had a history of viral myocarditis at the age of 5 months. A CXR showed enlargement of her cardiac silhouette. However, she was asymptomatic from a cardiovascular standpoint and zidovudine therapy was not interrupted. Several weeks after appearance of the S₃ gallop, her cardiac status was reevaluated. At that time, the gallop was no longer discernible; clinically, she was asymptomatic and active.

One child has died while participating in the study. This 12 year old with severe hemophilia died of liver failure 5 months after enrollment in the study. Liver dysfunction had been apparent at the time of entry into the protocol. His zidovudine dosing was modified 5 weeks after entry due to onset of pancytopenia. His liver function continued to deteriorate and zidovudine was discontinued 3 weeks prior to his death.

Subjective and objective clinical improvements such as weight gain, decreased lymphadenopathy and hepatosplenomegaly, increased appetite and activity level, and resolution of LIP in one child have been reported (16). Active clinical and laboratory monitoring continues for all patients enrolled.

2.22 Phase 1 Continuous Intravenous Infusion Study

This Phase 1 study was designed to evaluate the safety and pharmacokinetics of zidovudine administered by continuous intravenous infusion. Children who have symptomatic (Class P-2) HIV infection are eligible and are assigned to one of four dose groups. Three children must complete at least four weeks of dosing at the lowest dose level, without

development of unacceptable toxicity, prior to the enrollment of additional children at the next higher dose group. The following intravenous dose regimens are being utilized:

- A. 0.5 mg/kg/hr
- B. 0.9 mg/kg/hr
- C. 1.4 mg/kg/hr
- D. 1.8 mg/kg/hr

Children receive 24 weeks of zidovudine by continuous intravenous infusion at their assigned dose level. After 24 weeks, the children may be switched to oral dosing or may continue intravenous therapy. The intravenous dosing is administered by an infusion pump via an indwelling central venous catheter.

Twenty-two children have been enrolled into the study (two additional children from a previous protocol were also enrolled as described above. The participants range in age from one year to 13 years. Nine of the children acquired HIV infection by perinatal transmission and 11 acquired HIV infection through blood product transfusion (2 hemophiliacs). The children have participated in the study from 2 months to 14 months. Three patients were enrolled into dose group A (0.5 mg/kg/hr). No unacceptable toxicity was observed and 7 patients were subsequently enrolled into dose group B (0.9 mg/kg/hr). Seven patients have been entered in the third dose level (1.4 mg/kg/hr) and 5 children were entered into the fourth dose group (1.8 mg/kg/hr).

Twelve of the twenty-four patients have had their dose modified due to onset of hematologic abnormalities. Three patients had their dose reduced by one dose level due to anemia (1) and neutropenia (2). These children had their dose subsequently increased to their original level after the stabilization of hematologic parameters. Nine children had their dosing temporarily discontinued due to the onset of neutropenia. After stabilization of their neutrophil counts, dosing was restarted at the next lower dose group. In general, the children enrolled in this study had evidence of bone marrow compromise at entry. The mean hemoglobin and neutrophil count at entry were 9.3 gm/dl and 1875/mm³ respectively. Twelve children have received one or more transfusions for a decrease in hemoglobin. Seven of these 12 patients have received ≥ 3 red blood cell transfusions.

Six of the participants have developed opportunistic infections, including 5 cases of *Pneumocystis carinii* pneumonia (one with concurrent CMV pneumonia) and one disseminated *Mycobacterium avium-intracellulare* (MAI), which may have been present at entry into the study. Three of the five cases of PCP were fatal infections as was the disseminated MAI infection. Two additional children have died while participating in the study. One of these children died of presumed HIV-related cardiovascular disease (cardiomyopathy) and the other child succumbed to *Klebsiella* and enterococcal bacteremia.

Seven of the twenty-four patients have developed one or more serious bacterial infections (bacteremia or pneumonia) due to the following pathogens; *Staphylococcus*, *pneumococcus*, *Hemophilus influenzae*, *Streptococcus*, *Pseudomonas*, *Acinetobacter*, *enterococcus* and *Klebsiella*. Other minor bacterial infections continue to occur among the study participants, e.g., otitis media, sinusitis and cellulitis at the IV catheter site.

Subjective clinical improvements have been reported for the majority of children. These improvements include increased appetite, activity level and increased sense of well being. Decreased lymphadenopathy, hepato-splenomegaly, diarrhea and fevers have also been reported. Patients who have encephalopathic symptoms at entry have shown improvements in neurologic status. These improvements included increased IQ and motor skills, and improvements in gait, alertness, and articulation (17). Active clinical and laboratory monitoring continues for all enrolled patients.

2.3 Intravenous Immunoglobulin (IVIG)

The 3 principal biological activities of immunoglobulin are the binding of antigen, activation of the complement system, and binding of Fc receptors to promote phagocytosis.

Therapy for infectious diseases had its origin with the earliest work with aniline dyes leading to the present chemotherapeutic era. Passive immunization has undergone a similar although less dramatic evolution with the development of human immune serum globulin for hepatitis prophylaxis and the subsequent generalization of the method to generate hyperimmune products to prevent or ameliorate a number of transmissible diseases. Pooled human serum immunoglobulin was subsequently found to be effective replacement therapy for patients with a variety of primary disorders involving humoral immunity, especially for children with congenital agammaglobulinemia. There is speculation that, in addition to

providing simple antibody replacement, pooled immunoglobulin may influence the incidence of bacterial infections by reducing the immunosuppressive effects of immune complexes or by the action of antiidiotypic antibodies which might be modified somehow during the preparation of the pooled immunoglobulin itself.

One limitation of pooled immune serum globulin was the necessity for intramuscular administration, in order to avoid anti-complementary activity when given intravenously. Prophylaxis and especially treatment of established infections were physically limited by the patient's ability to accept large volumes of fluid intramuscularly. Early in the 1980s reduced, alkylated, and enzyme-digested immunoglobulin preparations without anticomplementary activity became available for intravenous infusion. These advances allowed true repletion of immunoglobulin to normal levels in immunodeficient patients. The newest generation of intravenous immunoglobulins has additional refinements. The native structure of the molecule is preserved without the phenomenon of aggregation. Whether this will be translated into improved activity and increased efficacy has yet to be determined.

The theoretical basis for intravenous immunoglobulin replacement generates from the immunological similarity of symptomatic pediatric HIV infection with primary humoral immunodeficiency. Antigenic challenge of the immature, naive and depressed immune system of HIV-infected infants results in impaired development of antigen-specific B- and T-cell clones that are required for the production of specific high-affinity, functional antibody.

Intravenous immunoglobulin (IVIG) use has been reported in HIV-infected children. Calvelli and Rubinstein used escalating doses (50-300 mg/kg) of IVIG during an 8-week period in a group of 14 HIV-infected children with recurrent bacterial infections with or without sepsis and compared their clinical course and laboratory parameters with 27 untreated HIV-infected children with recurrent bacterial infections (18). The principal finding of this study was that sepsis occurred in only 1/14 IVIG patients and in 18/27 comparison patients. Over 20 ± 9 months of follow-up, there were 3 febrile episodes lasting a week or longer in the IVIG and 26 in the comparison group. These investigators also claimed findings of increased CD4+ cells, decreased circulating immune complexes, enhanced mitogenic responses, and normalization of serum lactate dehydrogenase in IVIG-treated patients. Unfortunately, the magnitude of these changes was not reported. These authors also comment that survival was enhanced in IVIG-treated patients; however, no data are presented. This group also described a 70% mortality in an IVIG-treated group that had increased circulating immune complexes (19).

Siegal and Oleske, using IVIG (100mg/kg/wk), demonstrated enhanced survival in 19 patients when compared to 12 patients not receiving IVIG. Unfortunately, with prolonged follow-up, mortality tended to increase despite therapy (20). These two studies suggest IVIG prevents invasive bacterial infections in association with altered laboratory parameters. There is also the suggestion that IVIG therapy leads to improved quality of life. Unfortunately, each of these studies can be faulted for design. The retrospective nature of the information available suggests that some unintentional selection bias of treated (or untreated) patients may have influenced the final interpretation of the data. Furthermore, each of these treatment studies was begun at a time before the etiology of AIDS was known, and was undertaken with a product that may have contained antibody to HIV. The discovery of HIV and the screening of donors may have changed the composition of the IVIG available.

When given to a small number of HIV-infected children with pulmonary lymphoid hyperplasia (lymphoid interstitial proliferation) in combination with steroids IVIG was associated with improved chest roentgenograms, and no increased infection rate was observed in this patient group.

However, pulmonary interstitial proliferation is a fundamentally different disease entity, with a relatively better prognosis than other AIDS-related diseases in children (22); the data abstracted above do not prove that IVIG prevents bacterial infections, prolongs survival or enhances the quality of life. They do, however, provide a strong rationale for a controlled trial of IVIG in conjunction with zidovudine treatment.

3.0 STUDY OBJECTIVES

- 3.1 Evaluate the clinical, immunologic and virologic effects of zidovudine plus placebo as compared with zidovudine plus IVIG in children with symptomatic HIV infection by using the following criteria:

3.11 Primary

- 3.111 Reduction in frequency of "serious bacterial infections", defined as: meningitis, bacteremia, pneumonia, osteomyelitis, septic arthritis, acute sinusitis, acute mastoiditis, and abscess of an internal organ.

3.12 Secondary

- 3.121 Reduction in frequency of other bacterial, opportunistic, and viral infections.
- 3.122 Prolongation of survival.
- 3.123 Comparative tolerance of the two regimens.
- 3.124 Safety and tolerance of oral zidovudine 180mg/m² q6h administered for a minimum of 100 weeks to symptomatic HIV positive children 3 months to 12 years of age.
- 3.125 Safety and tolerance of IVIG when administered every 28 days in a dose of 400mg/kg to children receiving zidovudine.
- 3.126 Slowing of the progression of HIV disease as measured by:
 - p24 antigen
 - Immunologic measures: CD4+ cells, T4/T8 ratio, CD8 cells, gamma globulin levels
 - Age-appropriate physical growth (absence of failure to thrive - refer to 6.1511 for definition of failure to thrive)
 - New cardiomyopathy (as diagnosed by echocardiogram)
 - LIP as defined by the protocol
 - Progression to AIDS for patients entering with ARC (see Appendix I)
 - Renal disease (non-infectious)
 - Hepatitis and other hepatic disease
 - Non-infectious diarrhea (as in 6.1512)
 - Nonspecific indicators of HIV disease: lymphadenopathy, hepatosplenomegaly, and HIV encephalopathy as defined in Appendix II

4.0 INVESTIGATORS/FACILITIES

This will be a multicenter study open to all NIAID-sponsored ACTUs and NICHD-sponsored centers.

5.0 STUDY OUTLINE

This multicenter, randomized Phase III trial is designed to evaluate the safety and efficacy of oral zidovudine plus IVIG versus zidovudine plus placebo (albumin) administered for a minimum of 100 weeks. Two

hundred and fifty (250) children, 3 months to 12 years of age, with symptomatic HIV infection will be enrolled into the protocol. The study will be conducted on an outpatient basis. All participants will receive oral zidovudine at a dose of $180\text{mg}/\text{m}^2$ q6h. This dose was selected on the basis of pharmacokinetic projections and dose modification data from the Phase I study. A dose of $180\text{mg}/\text{m}^2$ will provide a 24 hour AUC (area under the plasma-concentration time curve) comparable to a regimen of 250mg q4h in adults. This regimen will also allow dose modification (in a range up to 30%) to the lowest dose utilized in the phase I study which indicated possible clinical benefit.

IVIG or intravenous placebo will be administered every 28 days. Patients will be followed for the development of serious bacterial infection, as well as for a number of secondary objectives relating to safety, tolerance, progression of HIV-associated disease, and survival.

6.0 PATIENT SELECTION

Reliability

6.1 Inclusion Criteria

- 6.11 Children with AIDS or ARC as defined below between 3 months and 12 years of age *(at time of enrollment)*
- 6.12 Children must have laboratory evidence of HIV infection as demonstrated by either a positive viral culture (blood or CSF) OR detectable serum p24 antigen OR two positive tests for HIV antibody in children > 15 months of age. HIV antibody must be determined by a federally licensed ELISA or IFA test and be confirmed by Western blot.
- * 6.13 Children < 15 months of age who are thought to have acquired HIV through perinatal transmission and whose only laboratory evidence of HIV infection is a positive antibody test must also have abnormal age-adjusted immunoglobulin levels (IgG , IgA , IgM). *Outside own lab values -*
- 6.14 AIDS:
 - 6.141 Children must have clinical evidence of HIV infection as demonstrated by the presence of one or more of the definitively or presumptively diagnosed indicator diseases as defined in the CDC Surveillance definition for AIDS (August 1987 Revision - refer to Appendix I).

Note: Children with LIP are excluded from enrollment unless they have had additional AIDS-defining opportunistic infections, meet ARC

If LIP alone
have all
3 criteria

Require

criteria below, have had two or more serious bacterial infections in the 12 months prior to study entry, or have evidence of HIV encephalopathy (refer to Appendix II for encephalopathy definition), or are currently on supplemental oxygen and steroids with a pre-treatment $P_{aO_2} < 70$ mmHg (room air). Children with LIP and with ARC, as defined by this protocol, are eligible for inclusion.

6.15 ARC:

6.151 Children who have either two of the major criteria or one of the major and at least one of the minor criteria within two months prior to entry.

6.1511 Major criteria are defined as follows:

If ON TPN >
2 mos before entry
& now not FT, etc.

KOH docum.
not necessary

* Failure to thrive, defined as a child who crosses two percentile lines on the growth chart or a child who is in less than the fifth percentile for height and weight and does not follow the growth curve. (Refer to Appendix III for growth chart.)

* Persistent (≥ 2 months) or recurrent oral candidiasis despite appropriate topical therapy.

* ≤ 500 CD4+ cells within three weeks prior to entry into protocol. (A second CD4+ determination will be done at entry in order to establish patient's baseline.)

If only minor
crit. is lymphadenopathy
then major must be
FT, etc.

6.1512 Minor criteria are defined as follows:

* Diarrhea (≥ 3 loose stools/day) that is either persistent (> 3 months) or recurrent (≥ 2 episodes resulting in dehydration within a 2 months period).

* Lymphadenopathy (> 0.5 cm) at 2 or more noncontiguous sites. Note: If this is the only minor finding, the child must have at least 1 of the first 2 major findings above.

* Organomegaly (hepatomegaly and/or splenomegaly).

* Cardiomyopathy.

- * Nephropathy manifested by nephrotic syndrome without evidence of renal failure.
- * Two or more episodes of herpes stomatitis or one or more episodes of herpes zoster within a 1 year period.
- * ^{HIV} ~~AIDS~~-associated ~~immune~~ thrombocytopenia ^a.
~~purpura (ITP)~~.

- 6.16 Absence of acute opportunistic infection at time of entry. Children receiving maintenance therapy, including amphotericin B for fungal disease or INH/rifampin for specific tuberculosis treatment, will be eligible. *Disallowed - ketoconazole, acyclovir for maintenance.*
- 6.17 Children receiving prophylaxis treatment for a previous episode of laboratory documented Pneumocystis carinii pneumonia (PCP) may remain on such therapy and will be eligible for inclusion in this protocol. However, patients receiving trimethoprim/sulfamethoxazole (TMP/SMX) for PCP prophylaxis will follow the TMP/SMX regimen as outlined in section 7.43. *Acyclovir, pentamidine, if drug not refused by the study, don't charge to the grant.*
- 6.18 Absence of bacterial infections requiring treatment at the time of entry.
- 6.19 Parent or guardian available to give written informed consent.

*Prophylaxis only
for documented
PCP - must have
seen organisms*

6.2 Exclusion Criteria

- 6.21 Children with LIP not requiring steroids and supplemental oxygen, or other lymphoproliferative diseases (e.g., parotitis), as their sole clinical evidence of HIV infection.
- ✓ 6.22 Children who have received other antiretroviral agents such as ribavirin or ddC within 4 weeks of entry. *Children may be/have been on zidovudine. Ribavirin allowed for anti therapy on study.*
- ✓ 6.23 Children who have received immunomodulating agents such as interferons, isoprinosine, or IL-2 within 4 weeks of entry.
- ✓ 6.24 Children who have received immunoglobulin within 4 weeks of entry.
- 6.25 Children with known hypersensitivity to immunoglobulin.

6.26 Children who have received the following within 4 weeks of entry:

6.261 Any other experimental therapy.

6.262 Drugs which cause prolonged neutropenia or significant nephrotoxicity.

6.27 Children receiving antibacterial prophylaxis for otitis, sinusitis, or urinary tract infection. Children receiving prophylaxis treatment for PCP prior to the first episode of laboratory documented PCP, will discontinue treatment.

If Rx sinusitis > 2 weeks. Must check c. Steve Spector
6.28 Pregnancy (pubertal females must be screened for possible pregnancy).

6.29 Children with any of the following laboratory findings within 4 weeks prior to entry:

6.291 A total bilirubin > 3 times upper limit of normal.

6.292 SGOT > 10 times upper limit of normal.

6.293 An estimated creatinine clearance < 50ml/min/1.73m².

6.294 Absolute neutrophil count (polys plus bands) < 1000 cells/mm³.

6.295 Hematocrit < 24% (Hgb < 8.0gm/dl).
Note: Patients may be transfused.

6.296 Platelet count < 75,000/mm³ (except for HIV associated thrombocytopenia for which thrombocytopenia will not be an exclusion).

6.30 Children with active HIV thrombocytopenia whose Investigator believes IVIG therapy is required.

If IVIG necessary to Rx & platelets, don't enroll child
6.31 Active alcohol or drug abuse.

6.32 Children in whom intravenous access cannot be established or maintained, or whose parent/guardian will not authorize such access.

6.3 Demographics of Patient Population

6.31 Age: 3 months to 12 years.

6.32 Sex: no restriction.

*2 sets of entry labs.
One done within 3 weeks of beginning.*

6.4 Number/Source/Management of Patients

- 6.41 Number of participants: 250 children will be enrolled in the study.
- 6.42 Source of patients: This will be a multicenter trial. HIV-infected children followed by or referred to a study center will be evaluated sequentially for potential enrollment. All children should be followed by their original study center for the duration of the trial.
- 6.43 Management of patients: This will be an outpatient study conducted over a minimum 100-week period. The participants will be evaluated weekly for the first 4 weeks, every 2 weeks for the subsequent 8 weeks, and monthly thereafter.

6.5 Informed Consent

All parents/guardians (and children when appropriate) will be given information about the general intent and rationale of the study, as well as the known toxicity and efficacy of zidovudine and IVIG in adults and children.

All parents/guardians must give written informed consent. The consent will specify the parent/guardian's freedom to withdraw the participant from the trial at any time without compromise of the child's regular medical care (See Appendix XII).

7.0 STUDY MEDICATION, DOSAGE, ROUTE AND DURATION OF ADMINISTRATION7.1 How Supplied, Storage and Administration7.11 Zidovudine

Zidovudine will be provided by Burroughs Wellcome Co. through the NIH as a sterile filtered aqueous solution at a concentration of 20mg/ml.

7.12 Intravenous immunoglobulin (IVIG)

IVIG is pooled human immunoglobulin which will be provided by Cutter Laboratories through the NIH as 50 ml vials. It is a 5% solution of primarily gammaglobulin in a 10% maltose solution to achieve isotonicity at a pH of 4.25. It contains no preservatives and must be stored refrigerated at 2-8°C. Each vial is intended for single use entry only.

Each milliliter (ml) of IVIG contains approximately 50mg of protein, not less than 98% of which has the

*AZT: 800 mg / bottle
bec. highly conc.
concentrated. Disp.
enough for 1 vial.*

*100mg caps. Cutter
only - must be
within 10% dosing
range.*

*logistics
of processing
1000 - filtering.
Eliz. Moore.*

-Prepackage AZT-

electrophoretic mobility of gammaglobulin. Not less than 90% of the gamma globulin is IgG. Also present are traces of IgA and IgM. The distribution of IgG subclasses is similar to that found in normal serum. The buffer capacity of the study drug is 16.5 mEq/l of solution (approximately 0.3 mEq/gm of protein). The calculated osmolality is 309 milliosmoles per kilogram of solvent (water) and the osmolarity is 278 milliosmoles per liter of solution.

IVIG is made by cold ethanol fractionation of large pools of human plasma. Each individual unit of plasma used in the pool has been tested and found to be nonreactive for hepatitis B surface antigen (HBsAg) and HIV antibody by FDA-approved methods.

7.13 IV Placebo

A preparation consisting of 0.1% albumin in 10% maltose which cannot be visually distinguished from IVIG. It will be provided by Cutter Laboratories.

The placebo solution must be filtered in the pharmacy with a 5 micron filter prior to administration. Infusions should commence promptly after vial entry, with the material being brought to room temperature prior to administration.

7.2 Preparation and Administration (See Appendices X, XI, and Pharmacist's Manual for details.)

7.21 Blinding of Study Regimen

Children will be randomized to receive either pooled IVIG or placebo which appears identical. Containers for IV administration and labelling must be indistinguishable.

7.22 Zidovudine

All children will receive oral zidovudine at a dose of 180mg/m² q6h. The sterile solution will be mixed with 4-6 oz. of juice (apple or orange) or water for oral dosing. Zidovudine will be dispensed on a weekly basis for the first 4 weeks of therapy, biweekly for the subsequent 8 weeks, and monthly thereafter. The study center pharmacy or study coordinator will be responsible for dispensing the study medication to each parent/guardian. All dispensed vials (used or unused) must be returned to the study center by the parent/guardian.

7.23 IVIG

The dose of IVIG will be 400mg/kg (3ml/kg) of body weight administered by intravenous infusion. It will not be mixed with any other fluids or medications. It must be filtered in the pharmacy with a 5 micron filter prior to infusion. It will be administered in such a way that D5W is piggybacked for immediate availability in the event the study drug infusion needs to be interrupted or discontinued.

While multiple lots will be used in the study, samples from each lot will be stored to allow later assessment of antibody content if so desired. Patients will not necessarily receive the same lot throughout the study.

7.231 Pre-medication: Benadryl and/or acetaminophen may be administered before and during the infusion in patients previously demonstrating mild reactions or during infusion if a reaction occurs.

7.232 Rate of infusion: When the patient is resting comfortably, the infusion will be started at a rate of 0.01-0.02 ml/kg/minute. If after 15-30 minutes there are no adverse effects, the rate may be gradually increased to 0.02-0.04 ml/kg/minute, and then if well tolerated, the infusion rate may be gradually increased to 0.04-0.06 ml/kg/minute. If well tolerated, the infusion rate may then be increased to a maximum of 0.08 ml/kg/minute.

Caution should be used in any patient requiring careful management of fluid status, such as patients in congestive heart failure or renal failure.

7.233 Possible adverse reactions: Generally, adverse reactions to IVIG are related to the rate at which they are infused. If mild signs or symptoms of adverse effects are seen, the rate of infusion of the test preparation should be halved to see if the signs/symptoms disappear. If the lowered infusion rate is tolerated without problems for 30 minutes, the infusion rate may be increased to the previous rate. If adverse effects are more than "mild," the infusion should be interrupted until the adverse effects have disappeared for approximately 30 minutes, after which time the infusion may be cautiously restarted at 0.01 ml/kg/minute.

Adverse reactions attributed to IVIG include fever; chills; backache; flushing - redness or swelling of hands and feet; emesis; muscle aches; fatigue; changes in vital signs; urticaria, itching; and rarely, anaphylaxis.

7.24 IV Placebo

Albumin prepared for investigational purposes will be given in a volume which corresponds to an equivalent dose of IVIG at 400mg/kg (i.e., 8ml/kg/dose), and will be administered exactly per the above protocol for the administration of IVIG. Albumin placebo must be filtered in the pharmacy with a 5 micron filter prior to infusion. Therefore, an in line filter is not recommended.

No adverse reactions from the placebo are expected; in other studies in which it was used, no adverse reactions were reported.

7.25 Basis for Calculation of Study Drug Doses

Body surface area (m^2) and weight will be recalculated every 8 weeks and doses of zidovudine and IVIG/placebo will be adjusted accordingly.

7.3 Medication Dispensing Records

Detailed dispensing instructions and medication dispensing records will be provided in the Pharmacist's Manual.

7.4 Concurrent Medications

7.41 Concomitant medication should be kept to a minimum.

7.42 The use of antibacterial agents for ^{prophylaxis of} bacterial infections such as otitis media is prohibited. Prophylaxis for Pneumocystis carinii pneumonia (PCP) in children who have not had a previous laboratory documented episode is prohibited. However, children who have had or develop a laboratory documented episode of PCP, may receive trimethoprim/sulfamethoxazole (TMP/SMX) or an alternative treatment for continuous PCP prophylaxis. Patients receiving TMP/SMX for PCP prophylaxis will follow the TMP/SMX regimen as outlined in section 7.43. TMP/SMX will be limited to three days a week.

re: Tolerance
but Symp.

7.43 A regimen of TMP, 75 mg/ m^2 per dose given BID, 3 times a week (MWF schedule) and SMX, 375 mg/ m^2 per dose given BID, 3 times a week (MWF schedule) is recommended. Children who are allergic or cannot tolerate TMP/SMX treatment may

receive alternative therapy. Children must be monitored closely for possible toxicity due to combination therapy with zidovudine.

7.44 Drugs that are metabolized by hepatic glucuronidation may alter the metabolism of zidovudine and should not be used chronically (i.e., more than 24 hours) without notifying study physician/coordinator. Acetaminophen is allowed for short term fever and pain management. Study patients should not take acetaminophen on a chronic basis or for 72 hours without contacting the Investigator.

7.45 Children should be immunized according to current ACIP guidelines (23).

7.5 Parents/Guardians

Parents/guardians will receive instructions as to the appropriate administration of study medication (Appendix IV). Parents/guardians must demonstrate the ability to dispense the zidovudine solution prior to receipt of the child's drug supply.

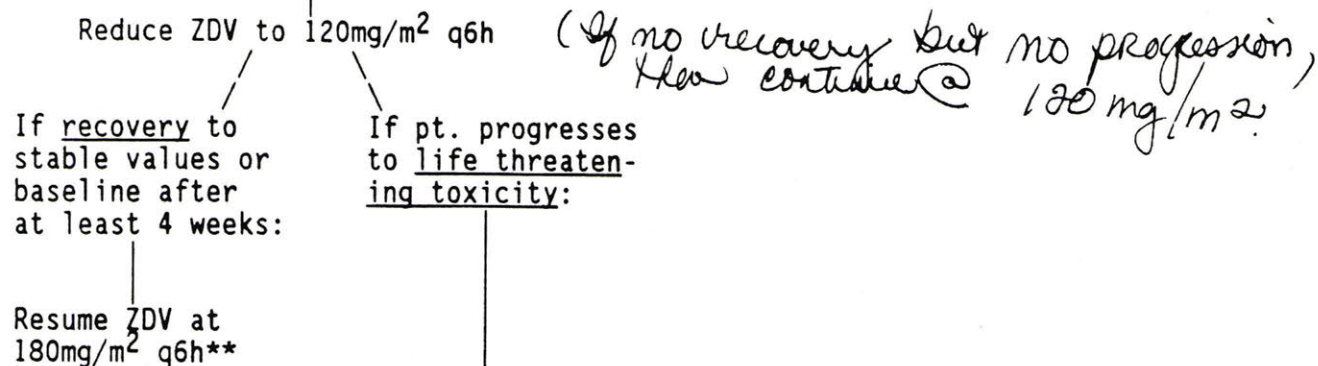
8.0 DOSE MODIFICATION OF ZIDOVUDINE FOR TOXICITY (See Appendix V)

8.1 Dose Modification for Hematologic Toxicity and Progressive Bone Marrow Suppression

<u>Definition</u>	<u>ANC</u>	<u>HGB</u>	<u>Platelets</u>
Stable Values or baseline	$\geq 1000/\text{mm}^3$	$\geq 8.0 \text{ gm/dl}$	$\geq 75,000/\text{mm}^3$
Moderate Toxicity	500-999/ mm^3	$< 8.0 \text{ gm/dl}$ or 3 gm decrease	25,000 - 74,999/ mm^3 *
Life Threatening Toxicity	$< 500/\text{mm}^3$ on 2 successive determinations 24 hours apart, occurring more than one week after dose reduction or when patient is on full dose.	Transfusion dependence (RBC) alone will not lead to discontinuation of drug.†	$< 25,000/\text{mm}^3$

* Patients with HIV thrombocytopenia are excluded from ZDV dose reduction for documented isolated thrombocytopenia.

† Children who become transfusion dependent (RBCs) because of bone marrow suppression are permitted to continue in the study.

Moderate Hematologic ToxicityLife Threatening Hematologic Toxicity***

Temporarily D/C ZDV for a maximum of 4 weeks - check lab values weekly

If recovery to moderate toxicity, stable values or baseline:

Resume ZDV at $120\text{mg}/\text{m}^2$ q6h

If patient lab values return to stable or baseline values after 4 weeks on the $120\text{mg}/\text{m}^2$ q6h dose:

Resume ZDV at $180\text{mg}/\text{m}^2$ q6h**

If no recovery to moderate toxicity, stable values or baseline:

Permanently off drug; study follow-up required (see Section 9.1)

** Patients experiencing a second episode of moderate toxicity must remain on the reduced dose level ($120\text{mg}/\text{m}^2$ q6h) until the end of study.

***A third episode (more than 2 episodes) of life threatening hematologic toxicity will result in permanent discontinuation of study therapy (see Section 8.11).

If PT reduced XZ, then never back to full.

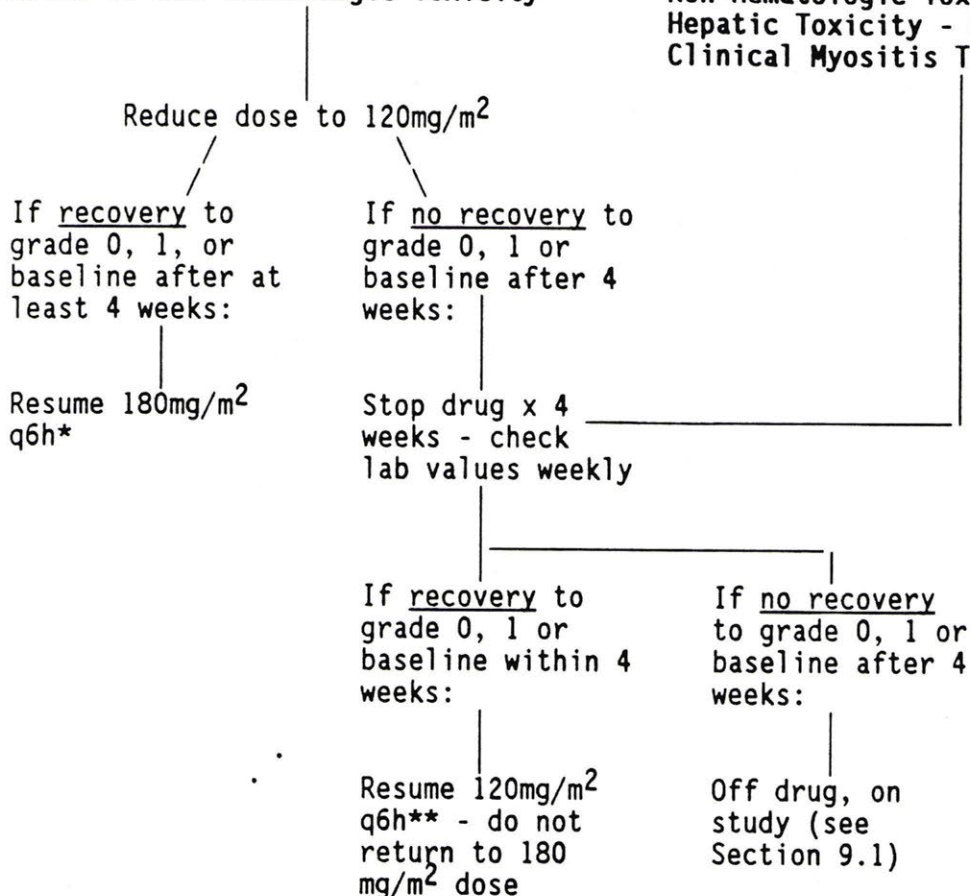
- 8.11 IVIG or albumin will be continued without interruption. However, children experiencing more than 2 episodes of toxicity requiring dose discontinuation and whose platelet and neutrophil counts fail to stabilize off zidovudine, will be permanently discontinued from study therapy (see Section 9.1).
- 8.12 Children receiving prophylactic therapy for a laboratory documented episode of PCP, must be monitored closely for possible toxicity due to combination therapy with zidovudine. If toxicity develops and zidovudine dose reduction is required, the prophylactic therapy will be temporarily discontinued. Prophylactic therapy will be resumed when the child's lab values stabilize on the reduced zidovudine dose.

8.2 Dose Modification for Non-hematologic Toxicities

<u>Toxicity</u> <u>Grade</u>	0	1	2	3	4
Hepatic Toxicity (SGOT)	<1.0 x N ¹	1.0-1.9 x N or ≥50 IU over baseline - whichever is greater	2.0-4.9 x N or ≥100 IU over baseline - whichever is greater	5.0-9.9 x N or ≥150 IU over baseline - whichever is greater	≥10.0 x N or ≥200 IU over baseline - whichever is greater
Clinical Myositis (CPK)	[-----No clinical evidence of myositis-----]				clinical evidence of myositis: >5 x N ¹ in the absence of any other cause such as recent IM injection/trauma, etc.*

¹N = upper limit of normal

* These findings of clinical myositis will be discussed with the Protocol Chairman before the patient is removed from study therapy.

Non-Hematologic Toxicity**Grade II Non-Hematologic Toxicity**

Non-Hematologic Toxicity Grade III-IV
Hepatic Toxicity - Grade III - IV⁺
Clinical Myositis Toxicity - Grade IV

+ See non-hematologic toxicity grade chart for hepatic toxicity in Section 8.2.

* Patients who experience a second episode of grade II toxicity requiring reduction to the 120 mg/m² dose, will remain at that dose and will not increase to the 180 mg/m² dose.

**Patients who reach this level must remain on the reduced dose (120 mg/m² q6h) until the end of study or as long as patients do not experience further toxicities (see Section 8.21).

8.21 IVIG or albumin will be continued without interruption. Children who experience 2 episodes of grade 3-4 non-hematologic toxicity requiring zidovudine interruption, will be removed from study therapy (see Section 9.1).

8.22 Children receiving prophylactic therapy for a laboratory documented episode of PCP, must be monitored closely for possible toxicity due to combination therapy with

zidovudine. If toxicity develops and zidovudine dose reduction is required, the prophylactic therapy will be temporarily discontinued. Prophylactic therapy will be resumed when the child's lab values stabilize on the reduced zidovudine dose.

9.0 TREATMENT DISCONTINUATION

Pt. is on study 1) until death
2) refuses phone call
3) to two years.

- 9.1 All patients who discontinue study therapy permanently will be followed monthly with a phone call and every three months with a clinic visit until such time that they would have completed the required time on protocol (100 weeks), in order to follow the development of serious bacterial infections, AIDS-defining opportunistic infections and malignancies, and survival. All clinical and laboratory monitoring which would have been performed at the final visit (week 100) must be obtained at the time of study discontinuation. In addition to clinic visits, a monthly follow-up form will be completed when clinic visits are not scheduled.

Patients will be discontinued from all study medication (zidovudine and IVIG/PLC) for any of the following reasons, regardless to which therapy the toxicity is attributed. However, such patients who are discontinued from study therapy will be followed for ascertainment of study endpoints.

- 9.11 Severe allergic reaction such as exfoliative erythroderma or anaphylaxis.

- 9.12 Patient non-compliance: a child who is not adhering to the dosing regimen as defined by missing 2 consecutive IVIG/placebo doses or 3 doses/year and/or missing zidovudine for two consecutive months or 3 months/year.

- 9.13 A child who requires treatment with an experimental agent.

- 9.14 A child who has two or more serious bacterial infections while on the study. *CDC criteria: documented pneum.*
& (+) blood culture. Mastoiditis is serious.

- 9.15 At the request of the parent, legal guardian, investigator, or sponsor.

- 9.16 Drug toxicities under the conditions described in sections 8.1 and 8.2.

- 9.2 Except in the case of an anaphylactic reaction, the investigator will not be informed as to whether the child had been assigned to the IVIG or placebo group, since data collection on the child will need to continue in a masked manner.

*{ bronch. or
open lung bx*

10.0 RANDOMIZATION METHODS AND PROCEDURES FOR IVIG AND PLACEBO

Placebo and IVIG will be randomly assigned to patients as they enter the study, with equal numbers in the treatment groups.

10.1 The data center will conduct the randomization and communicate treatment assignments to the clinical center in coded form so that personnel responsible for treatment administration and patient follow-up assessments are blinded to the assigned therapy. Patients will be stratified at entry for (1) history of one or more serious bacterial infections within two years prior to entry, defined as: meningitis, bacteremia, pneumonia, osteomyelitis, septic arthritis, acute mastoiditis, acute sinusitis, and abscess of an internal organ, (2) prior zidovudine therapy, and (3) current prophylaxis with trimethoprim/sulfamethoxazole (TMP/SMX). The data center will maintain a record of each patient's treatment assignment and, for IVIG patients, drug lot numbers. To accommodate the breaking of a code in an emergency, secured treatment assignments will be on file at each clinical center.

11.0 CLINICAL EVALUATION (See Appendix VI)

Children meeting eligibility criteria and whose parent/legal guardian provides written consent to participate in the study will be enrolled. Clinical monitoring of the study participants will be completed on a weekly basis for the first 4 weeks, biweekly for the subsequent 8 weeks, and every 4 weeks thereafter. Pre-entry evaluations must be completed within 21 days prior to entry (start of study medication). The following clinical evaluations will be completed:

11.1 Pre-entry, entry, and every 8 weeks thereafter

Comprehensive physical exam including assessment of lymphadenopathy, organomegaly, growth chart documentation, age-related neurologic exam.

11.2 Pre-entry, entry, and every visit thereafter 20 visits

Objective signs (e.g., height, weight and vital signs)
Assessment of HIV infection-associated symptoms such as fever, activity level, dyspnea, headache, etc.

11.3 Pre-entry, Weeks 12, 24, 40, 56, 80, and 100 (selected sites only - see 11.10)

Neuropsychiatric testing and psychomotor evaluation (Appendix VII).

All children will be administered the appropriate tests for their specific age group at baseline. These tests administered at baseline will be repeated at the next testing period. If the second testing session is a transition period to the higher age bracket, the child will be administered the new battery of tests in addition to the old battery of tests. The child will then proceed with the appropriate age schedule.

If a child in the 30 months through 5 years age group presents delay at baseline testing with the McCarthy Scales of Childrens' Abilities Test, then the Bayley Scales of Infant Development Test will be administered. If a child in the 6 through 12 years age group presents delay at baseline testing with the Wechsler Intelligence Scale for Children (WISC-R) Test, then the McCarthy Scales of Childrens' Abilities Test will be administered. At follow-up (6 months), the baseline test should be repeated in addition to the age appropriate test. Since the Bayley is only normed up to 30 months, the test score may need to be converted to a mental age ratio rather than using the deviation IQ's.

- 11.4 Entry, Weeks 36 and 88 if abnormal at entry (selected sites only - see 11.10)

CT scan (without contrast) of the brain. Repeat at weeks 36 and 88 only if entry scan abnormal. Additional CT scans and/or MRI scans may be obtained as clinically indicated.

- 11.5 Entry, Weeks 48 and 100

Chest X-ray (posteroanterior and lateral). Children with concurrent LIP will require CXRs at 12-week intervals. Additional CXRs may be obtained as clinically indicated.

- 11.6 Pre-entry; Repeat as clinically indicated (selected sites only - see 11.10)

Lumbar puncture: CSF for protein, glucose and cell count with differential. As clinically indicated, bacterial, viral and fungal cultures should be obtained as well as specific antigen assays e.g. (cryptococcal and *Haemophilus influenzae* B). CSF for isolation of HIV and p24 antigen determination will be collected at pre-entry and as clinically indicated. Pre-entry CSF and serum for culture and p24 antigen should be obtained on the same day.

- 11.7 Entry; Weeks 48 and 100 only for children with cardiomyopathy

EKG (all children). Repeat at weeks 48 and 100 only in children with clinical cardiomyopathy. Additional exams may be obtained as clinically indicated.

11.8 Entry; Weeks 48 and 100 only for children with cardiomyopathy - (selected sites only - see 11.10)

Echocardiogram at entry. Repeat at weeks 48 and 100 only in children with clinical cardiomyopathy. Additional exams may be obtained as clinically indicated.

11.9 Other Clinical Evaluations

11.91 Development of opportunistic and other infections or AIDS-related neoplasms will be documented for the duration of the study. Laboratory documentation (e.g., culture, biopsy) of the pathogen/neoplasm is mandatory. A presumptive diagnosis will be accepted only if the diagnosis is based upon the guidelines in Appendix III of the CDC surveillance definition for AIDS (refer to Appendix I of this protocol).

11.92 Concurrent medications, receipt of blood products, and adverse experiences will be recorded on a continuous basis (i.e., upon drug administration or occurrence of event). Prophylaxis for oral candidiasis, or chronic otitis media or other infections (sinusitis, UTI) is prohibited. Likewise, the administration of immunoglobulin therapy is prohibited except for single dose exposure prophylaxis. PCP prophylaxis as outlined in sections 7.42 and 7.43 is allowed. Medications and blood products administered within 4 weeks prior to entry should also be recorded.

11.93 Children who experience a serious adverse event (toxicity grades 3-4) will be evaluated clinically within 24 hours. This initial 24-hour evaluation may be completed by the patient's own physician at a local clinical facility or at the primary study center. All pertinent medical records must be retrieved from the local facility by the study center.

11.94 Isoenzyme evaluations will be obtained at the same time as CPK evaluations in children with clinical evidence of myositis.

11.10 Definitions of "selected sites only":

11.101 For the 4 evaluations indicated above (LP, CT scan, neuropsychiatric testing and echocardiogram), any site may elect to perform any, all, or none of these tests;

→ Neuropsych & CT. Ask permission to delete pre-testing. Each portion filled in by Rita.

11.102 If a site chooses to do any test, the schedule of evaluations outlined in the protocol for that test must be followed (i.e. random testing is not allowed);

11.103 If a site chooses to do any test, they must do the test on ALL children enrolled at that site (i.e. no patient selection). Exceptions will be made for patients whose parents/guardians refuse lumbar punctures.

12.0 LABORATORY EVALUATIONS (Appendix VIII)

Laboratory evaluations will be completed according to the following schedule. All pre-entry evaluations must be completed within 21 days prior to (start of study medication).

12.1 Pre-entry, entry, and every visit thereafter

Hematologic Studies: CBC with differential, MCV, platelet count, and reticulocyte count.

12.2 Pre-entry, entry, and every 4 weeks thereafter

Urinalysis: routine urinalysis using a dipstick.

Chemistries: Serum creatinine, BUN, bilirubin (total), liver transaminases, LDH.

12.3 Pre-entry, entry, and every 8 weeks thereafter

CPK

12.4 Pre-entry, entry, Weeks 4, 12, 28, 44, 60, 76, and 100

T4 lymphocytes: Determination of absolute numbers of T-helper cells.

12.5 Pre-entry, entry, Weeks 4, 12, 28, 44, 60, 76, and 100

Virology: Samples for isolation of HIV from blood and for serum p24 antigen determination. CSF for isolation of HIV and p24 antigen determination will be collected at pre-entry, and as clinically indicated. Pre-entry CSF and serum for culture and p24 antigen should be obtained on the same day.

12.6 Pre-entry, entry, Weeks 16, 32, 48, 72, and 100

Immune function: Quantitative immunoglobulin levels (IgG, IgA, IgM), to be drawn prior to administration of IVIG/placebo during the course of the study.

12.7 Pre-entry, entry, and every month as indicated

Pulmonary: Oxygen saturation by oximetry for children with cardiac or pulmonary dysfunction. Additional samples may be obtained as clinically indicated.

12.8 Serum for storage; entry, Weeks 12, 24, 36, 48, 60, 72, 84, and 96

A minimum of 2 ml of sera in 0.5 ml aliquots will be frozen at -20°C for future studies.

12.9 Pre-entry

Serology: HIV antibody (see section 6.12 for details)

Pregnancy test for all female patients of childbearing potential.

Immune function (selected sites only - see 11.0): in vitro assays of cellular immune function will be performed at pre-entry and at the time of reactivation of cutaneous hypersensitivity. The following mitogens may be utilized: pokeweed, tetanus, candida, S. aureus, concanavalin A, phytohemagglutinin.

12.10 Optional

Pharmacokinetic analyses of zidovudine and its major metabolite, GAZT, may be performed at the study centers, according to defined methodology.

12.11 Optional Exam

A bone marrow biopsy may be performed in the event of serious hematologic toxicity.

Additional serum samples or urine samples (urinary GAZT levels) may be obtained for analysis of zidovudine levels in the event of a suspected drug-related serious adverse effect or in case of suspected non-compliance.

13.0 ADVERSE EXPERIENCES (See Appendix IX)

Adverse experiences will be reported as either associated with use of the drug or not associated with use of drug, based on the investigator's judgement.

Any serious, alarming or life-threatening reaction which occurs during this study, must be reported to the AIDS Program/AER Office within 24

hours, whether or not this reaction is considered to be related to the investigational drug.

Children who experience a serious adverse event will be evaluated within 24 hours of discontinuation of study medication. This initial 24-hour evaluation may be completed by the patient's own physician or a facility other than the primary study center. However, all pertinent medical records must be retrieved by the study center.

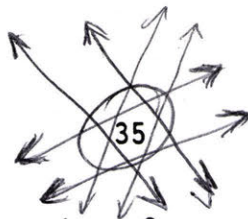
14.0 DATA COLLECTION AND MONITORING

Data collection forms will be provided for each patient. Study participants must not be identified by name on any study documents. Patients will be identified by the clinic assigned Patient Identification Number (PID) and Study Identification Number (SID) provided by the coordinating Center upon randomization. The investigator will allow the Coordinating Center monitor and the FDA to inspect study documents (e.g., consent forms, drug distribution forms, IRB approval) and pertinent hospital or clinic records for confirmation of data throughout the study period.

15.0 STUDY MONITORING SITE VISITS

- 15.1 Monitors from Burroughs Wellcome and Cutter may accompany the Coordinating Center monitor to initiate the study as well as visit at intervals for routine monitoring, which includes verification of source documents, drug accountability and storage, case report form data verification, and evaluation of study progress.
- 15.2 Site visits will be performed no less than twice each year by a physician employed by the Coordinating Center to ensure that all regulatory requirements for the use of investigational agents are being met. Records of IRB approvals will be examined.
- 15.3 Data audit site visits by staff of the Coordinating Center will occur no less than six times each year to monitor the quality of data collected. Patient charts will be examined on a spot check basis to evaluate the accuracy of data entered into the database.
- 15.4 Additional instructions concerning the recording of study data or the entry of such data into the computerized data base will be provided by the Coordinating Center.
- 15.5 Retention and Availability of Investigational Records

The investigator will maintain adequate records of the receipt and disposition of all the study drug, case report forms,



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10/24/88

patient consent forms, etc., for a period of two years after the IND is discontinued by NIAID or NDA approval of zidovudine and/or IVIG for the treatment of HIV- infected children, whichever is earlier. These records will be made available at reasonable times for inspection and copying if requested by a properly authorized employee of the Department of Health and Human Services in accordance with federal regulations.

15.6 Interim monitoring of data

Interim analyses will be performed to ensure the ethical integrity of the study. The results will be presented by the Coordinating Center to the Data and Safety Monitoring Board for review of toxicity and efficacy. Conditional power calculations, confidence intervals, and other biostatistical methods will be considered for quantifying the relative treatment effects.

16.0 BIOSTATISTICAL CONSIDERATIONS

The safety and tolerance of oral zidovudine plus either IVIG therapy or placebo will be evaluated by examining adverse experience data and clinical laboratory data. The clinical, immunologic and virologic effects of zidovudine and IVIG therapy will be evaluated according to the primary and secondary criteria described in section 3.0.

16.1 Sample Size

Assuming that serious bacterial infections occur in the zidovudine alone treatment group at a rate of 25% during the two year treatment period, 112 patients per group will be required to achieve 80% power using a 5% chi-squared test to detect a decrease from 25% to 10% in the zidovudine plus IVIG treatment group (24).

To allow for patients lost to follow-up, 125 patients per group (250 total) will be accrued.

16.2 Intention to Treat Analysis

To preserve the full advantages of the randomized design and to minimize the introduction of bias into the treatment comparisons, the primary hypotheses will be tested with the intention to treat rule, i.e., with all members of a randomized group who satisfy the on-study eligibility criteria after a blinded review of all patients, irrespective of early failure, study medication withdrawal, study group cross-over, or medication compliance.

16.3 Interim Analyses

An independent Data and Safety Monitoring Board will be convened to assess the progress of the trial at six month intervals during patient entry. Accrual of 250 patients is anticipated to require 1.5 years. With two years of additional follow-up, 6 interim analyses and one final analysis will be required. The O'Brien-Fleming p-values using a test to compare the incidence of serious bacterial infection for this situation are .001 for the first three looks, followed by .006, .015, .026, and .039 for the final analysis. Fleming proposed that a p-value of .001 be used whenever his method gives a p-value of .001 or less, and this convention will be followed for this trial.

Of primary interest for monitoring purposes is the time to occurrence of the first "event", where the "event" can be serious bacterial infection, development of an AIDS defining OI, or death. Statistical methods for the analysis of these data will include Cox's life-table regression model and the logrank test.

17.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this multicenter trial will be governed by AIDS Program policies. Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical sponsors prior to submission.

18.0 HUMAN SUBJECTS

The appropriate parent or guardian of study participants must sign an informed consent which will describe the objectives of the study and potential risks. This protocol requires prior IRB approval before any subject is entered into the study.

Potentially eligible subjects will be selected from participating ACTG study centers. Consecutive potential subjects will be evaluated to reduce internal selection bias.

All laboratory specimens, evaluation forms and reports will be identified by a coded number only to maintain patient confidentiality. All records will be kept in a locked file cabinet in the clinical research unit. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without the written permission of the patient, except as necessary for monitoring by the FDA, the pharmaceutical sponsors, or the National Institutes of Health.

19.0 BIOHAZARD CONTAINMENT

As the transmission of HIV can occur rarely through contact with contaminated needles, blood and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and handling of all specimens for this study in a clinical or laboratory setting, as currently recommended by the Centers for Disease Control.

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Revision of the CDC Surveillance Case Definition for Acquired Immunodeficiency Syndrome

*Reported by
Council of State and Territorial Epidemiologists;
AIDS Program, Center for Infectious Diseases, CDC*

INTRODUCTION

The following revised case definition for surveillance of acquired immunodeficiency syndrome (AIDS) was developed by CDC in collaboration with public health and clinical specialists. The Council of State and Territorial Epidemiologists (CSTE) has officially recommended adoption of the revised definition for national reporting of AIDS. The objectives of the revision are a) to track more effectively the severe disabling morbidity associated with infection with human immunodeficiency virus (HIV) (including HIV-1 and HIV-2); b) to simplify reporting of AIDS cases; c) to increase the sensitivity and specificity of the definition through greater diagnostic application of laboratory evidence for HIV infection; and d) to be consistent with current diagnostic practice, which in some cases includes presumptive, i.e., without confirmatory laboratory evidence, diagnosis of AIDS-indicative diseases (e.g., *Pneumocystis carinii* pneumonia, Kaposi's sarcoma).

The definition is organized into three sections that depend on the status of laboratory evidence of HIV infection (e.g., HIV antibody) (Figure 1). The major proposed changes apply to patients with laboratory evidence for HIV infection: a) inclusion of HIV encephalopathy, HIV wasting syndrome, and a broader range of specific AIDS-indicative diseases (Section II.A); b) inclusion of AIDS patients whose indicator diseases are diagnosed presumptively (Section II.B); and c) elimination of exclusions due to other causes of immunodeficiency (Section I.A).

Application of the definition for children differs from that for adults in two ways. First, multiple or recurrent serious bacterial infections and lymphoid interstitial pneumonia/pulmonary lymphoid hyperplasia are accepted as indicative of AIDS among children but not among adults. Second, for children < 15 months of age whose mothers are thought to have had HIV infection during the child's perinatal period, the laboratory criteria for HIV infection are more stringent, since the presence of HIV antibody in the child is, by itself, insufficient evidence for HIV infection because of the persistence of passively acquired maternal antibodies < 15 months after birth.

The new definition is effective immediately. State and local health departments are requested to apply the new definition henceforth to patients reported to them. The initiation of the actual reporting of cases that meet the new definition is targeted for September 1, 1987, when modified computer software and report forms should be in place to accommodate the changes. CSTE has recommended retrospective application of the revised definition to patients already reported to health departments. The new definition follows:

1987 REVISION OF CASE DEFINITION FOR AIDS FOR SURVEILLANCE PURPOSES

For national reporting, a case of AIDS is defined as an illness characterized by one or more of the following "indicator" diseases, depending on the status of laboratory evidence of HIV infection, as shown below.

I. Without Laboratory Evidence Regarding HIV Infection

If laboratory tests for HIV were not performed or gave inconclusive results (See Appendix I) and the patient had no other cause of immunodeficiency listed in Section I.A below, then any disease listed in Section I.B indicates AIDS if it was diagnosed by a definitive method (See Appendix II).

A. Causes of immunodeficiency that disqualify diseases as indicators of AIDS in the absence of laboratory evidence for HIV infection

1. high-dose or long-term systemic corticosteroid therapy or other immunosuppressive/cytotoxic therapy ≤ 3 months before the onset of the indicator disease
2. any of the following diseases diagnosed ≤ 3 months after diagnosis of the indicator disease: Hodgkin's disease, non-Hodgkin's lymphoma (other than primary brain lymphoma), lymphocytic leukemia, multiple myeloma, any other cancer of lymphoreticular or histiocytic tissue, or angioimmunoblastic lymphadenopathy
3. a genetic (congenital) immunodeficiency syndrome or an acquired immunodeficiency syndrome atypical of HIV infection, such as one involving hypogammaglobulinemia

B. Indicator diseases diagnosed definitively (See Appendix II)

1. candidiasis of the esophagus, trachea, bronchi, or lungs
2. cryptococcosis, extrapulmonary
3. cryptosporidiosis with diarrhea persisting > 1 month
4. cytomegalovirus disease of an organ other than liver, spleen, or lymph nodes in a patient > 1 month of age
5. herpes simplex virus infection causing a mucocutaneous ulcer that persists longer than 1 month; or bronchitis, pneumonitis, or esophagitis for any duration affecting a patient > 1 month of age
6. Kaposi's sarcoma affecting a patient < 60 years of age
7. lymphoma of the brain (primary) affecting a patient < 60 years of age
8. lymphoid interstitial pneumonia and/or pulmonary lymphoid hyperplasia (LIP/PLH complex) affecting a child < 13 years of age
9. *Mycobacterium avium* complex or *M. kansasii* disease, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
10. *Pneumocystis carinii* pneumonia
11. progressive multifocal leukoencephalopathy
12. toxoplasmosis of the brain affecting a patient > 1 month of age

II. With Laboratory Evidence for HIV Infection

Regardless of the presence of other causes of immunodeficiency (I.A), in the presence of laboratory evidence for HIV infection (See Appendix I), any disease listed above (I.B) or below (II.A or II.B) indicates a diagnosis of AIDS.

A. Indicator diseases diagnosed definitively (See Appendix II)

1. bacterial infections, multiple or recurrent (any combination of at least two within a 2-year period), of the following types affecting a child < 13 years of age:
 - septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media or superficial skin or mucosal abscesses), caused by *Haemophilus*, *Streptococcus* (including pneumococcus), or other pyogenic bacteria
2. coccidioidomycosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
3. HIV encephalopathy (also called "HIV dementia," "AIDS dementia," or "subacute encephalitis due to HIV") (See Appendix II for description)
4. histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
5. isosporiasis with diarrhea persisting > 1 month
6. Kaposi's sarcoma at any age
7. lymphoma of the brain (primary) at any age
8. other non-Hodgkin's lymphoma of B-cell or unknown immunologic phenotype and the following histologic types:
 - a. small noncleaved lymphoma (either Burkitt or non-Burkitt type) (See Appendix IV for equivalent terms and numeric codes used in the *International Classification of Diseases*, Ninth Revision, Clinical Modification)
 - b. immunoblastic sarcoma (equivalent to any of the following, although not necessarily all in combination: immunoblastic lymphoma, large-cell lymphoma, diffuse histiocytic lymphoma, diffuse undifferentiated lymphoma, or high-grade lymphoma) (See Appendix IV for equivalent terms and numeric codes used in the *International Classification of Diseases*, Ninth Revision, Clinical Modification)

Note: Lymphomas are not included here if they are of T-cell immunologic phenotype or their histologic type is not described or is described as "lymphocytic," "lymphoblastic," "small cleaved," or "plasmacytoid lymphocytic"

9. any mycobacterial disease caused by mycobacteria other than *M. tuberculosis*, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
10. disease caused by *M. tuberculosis*, extrapulmonary (involving at least one site outside the lungs, regardless of whether there is concurrent pulmonary involvement)
11. *Salmonella* (nontyphoid) septicemia, recurrent
12. HIV wasting syndrome (emaciation, "slim disease") (See Appendix II for description)

B. Indicator diseases diagnosed presumptively (by a method other than those in Appendix II)

Note: Given the seriousness of diseases indicative of AIDS, it is generally important to diagnose them definitively, especially when therapy that would be used may have serious side effects or when definitive diagnosis is needed

for eligibility for antiretroviral therapy. Nonetheless, in some situations, a patient's condition will not permit the performance of definitive tests. In other situations, accepted clinical practice may be to diagnose presumptively based on the presence of characteristic clinical and laboratory abnormalities. Guidelines for presumptive diagnoses are suggested in Appendix III.

1. candidiasis of the esophagus
2. cytomegalovirus retinitis with loss of vision
3. Kaposi's sarcoma
4. lymphoid interstitial pneumonia and/or pulmonary lymphoid hyperplasia (LIP/PLH complex) affecting a child < 13 years of age
5. mycobacterial disease (acid-fast bacilli with species not identified by culture), disseminated (involving at least one site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
6. *Pneumocystis carinii* pneumonia
7. toxoplasmosis of the brain affecting a patient > 1 month of age

III. With Laboratory Evidence Against HIV Infection

With laboratory test results negative for HIV infection (See Appendix II), a diagnosis of AIDS for surveillance purposes is ruled out *unless*:

- A. all the other causes of immunodeficiency listed above in Section I.A are excluded; AND
- B. the patient has had either:
 1. *Pneumocystis carinii* pneumonia diagnosed by a definitive method (See Appendix II); OR
 2. a. any of the other diseases indicative of AIDS listed above in Section I.B diagnosed by a definitive method (See Appendix II); AND
b. a T-helper/inducer (CD4) lymphocyte count < 400/mm³.

COMMENTARY

The surveillance of severe disease associated with HIV infection remains an essential, though not the only, indicator of the course of the HIV epidemic. The number of AIDS cases and the relative distribution of cases by demographic, geographic, and behavioral risk variables are the oldest indices of the epidemic, which began in 1981 and for which data are available retrospectively back to 1978. The original surveillance case definition, based on then-available knowledge, provided useful epidemiologic data on severe HIV disease (1). To ensure a reasonable predictive value for underlying immunodeficiency caused by what was then an unknown agent, the indicators of AIDS in the old case definition were restricted to particular opportunistic diseases diagnosed by reliable methods in patients without specific known causes of immunodeficiency. After HIV was discovered to be the cause of AIDS, however, and highly sensitive and specific HIV-antibody tests became available, the spectrum of manifestations of HIV infection became better defined, and classification systems for HIV infection were developed (2-5). It became apparent that some progressive, seriously disabling, and even fatal conditions (e.g., encephalopathy, wasting syndrome) affecting a substantial number of HIV-infected patients were not subject to epidemiologic surveillance, as they were not included in the AIDS

case definition. For reporting purposes, the revision adds to the definition most of those severe non-infectious, non-cancerous HIV-associated conditions that are categorized in the CDC clinical classification systems for HIV infection among adults and children (4,5).

Another limitation of the old definition was that AIDS-indicative diseases are diagnosed presumptively (i.e., without confirmation by methods required by the old definition) in 10%-15% of patients diagnosed with such diseases; thus, an appreciable proportion of AIDS cases were missed for reporting purposes (6,7). This proportion may be increasing, which would compromise the old case definition's usefulness as a tool for monitoring trends. The revised case definition permits the reporting of these clinically diagnosed cases as long as there is laboratory evidence of HIV infection.

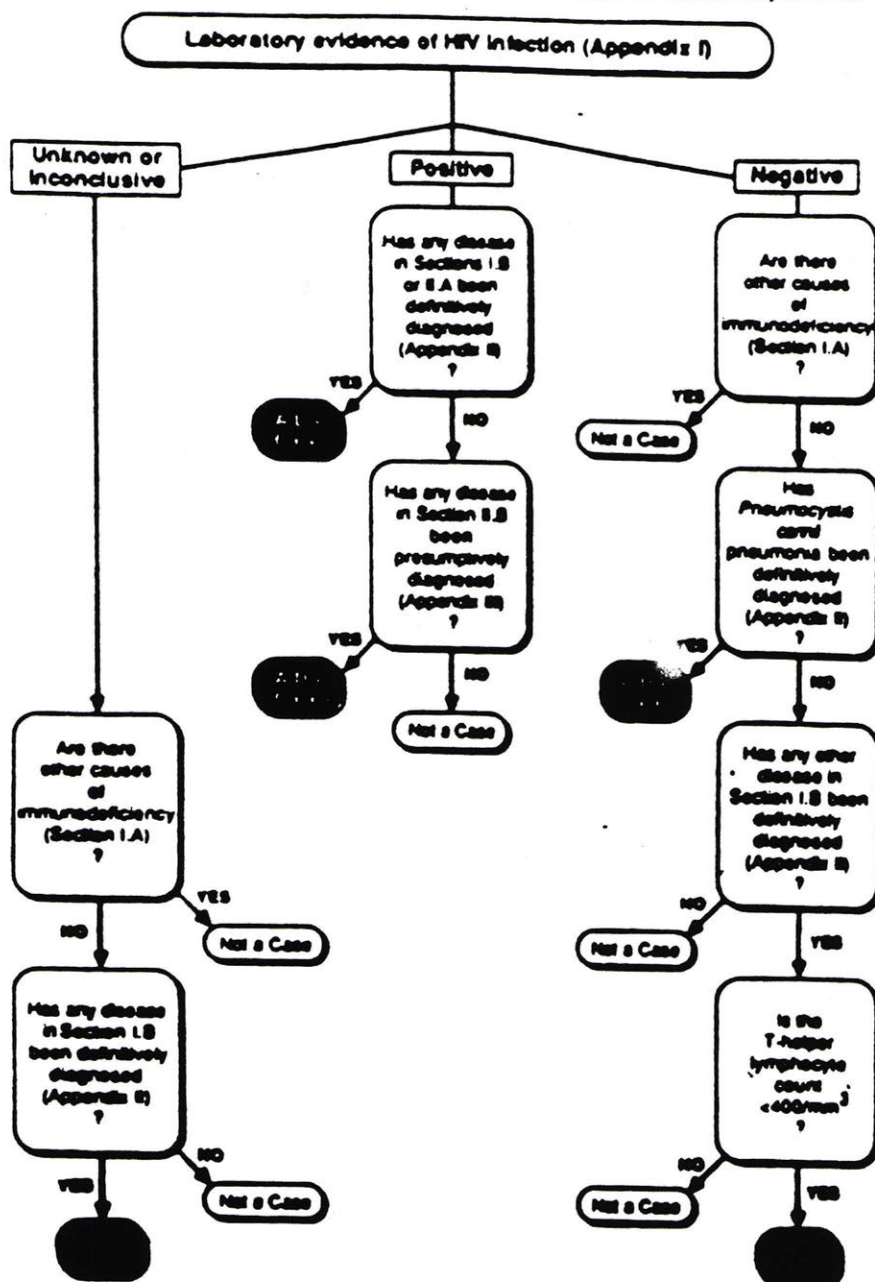
The effectiveness of the revision will depend on how extensively HIV-antibody tests are used. Approximately one third of AIDS patients in the United States have been from New York City and San Francisco, where, since 1985, < 7% have been reported with HIV-antibody test results, compared with > 60% in other areas. The impact of the revision on the reported numbers of AIDS cases will also depend on the proportion of AIDS patients in whom indicator diseases are diagnosed presumptively rather than definitively. The use of presumptive diagnostic criteria varies geographically, being more common in certain rural areas and in urban areas with many indigent AIDS patients.

To avoid confusion about what should be reported to health departments, the term "AIDS" should refer only to conditions meeting the surveillance definition. This definition is intended only to provide consistent statistical data for public health purposes. Clinicians will not rely on this definition alone to diagnose serious disease caused by HIV infection in individual patients because there may be additional information that would lead to a more accurate diagnosis. For example, patients who are not reportable under the definition because they have either a negative HIV-antibody test or, in the presence of HIV antibody, an opportunistic disease not listed in the definition as an indicator of AIDS nonetheless may be diagnosed as having serious HIV disease on consideration of other clinical or laboratory characteristics of HIV infection or a history of exposure to HIV.

Conversely, the AIDS surveillance definition may rarely misclassify other patients as having serious HIV disease if they have no HIV-antibody test but have an AIDS-indicative disease with a background incidence unrelated to HIV infection, such as cryptococcal meningitis.

The diagnostic criteria accepted by the AIDS surveillance case definition should not be interpreted as the standard of good medical practice. Presumptive diagnoses are accepted in the definition because not to count them would be to ignore substantial morbidity resulting from HIV infection. Likewise, the definition accepts a reactive screening test for HIV antibody without confirmation by a supplemental test because a repeatedly reactive screening test result, in combination with an indicator disease, is highly indicative of true HIV disease. For national surveillance purposes, the tiny proportion of possibly false-positive screening tests in persons with AIDS-indicative diseases is of little consequence. For the individual patient, however, a correct diagnosis is critically important. The use of supplemental tests is, therefore, strongly endorsed. An increase in the diagnostic use of HIV-antibody tests could improve both the quality of medical care and the function of the new case definition, as well as assist in providing counselling to prevent transmission of HIV.

FIGURE 1. Flow diagram for revised CDC case definition of AIDS, September 1, 1987



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APPENDIX I

Laboratory Evidence For or Against HIV Infection

1. For Infection:

When a patient has disease consistent with AIDS:

- a. a serum specimen from a patient ≥ 15 months of age, or from a child < 15 months of age whose mother is not thought to have had HIV infection during the child's perinatal period, that is repeatedly reactive for HIV antibody by a screening test (e.g., enzyme-linked immunosorbent assay [ELISA]), as long as subsequent HIV-antibody tests (e.g., Western blot, immunofluorescence assay), if done, are positive; OR
- b. a serum specimen from a child < 15 months of age, whose mother is thought to have had HIV infection during the child's perinatal period, that is repeatedly reactive for HIV antibody by a screening test (e.g., ELISA), plus increased serum immunoglobulin levels and at least one of the following abnormal immunologic test results: reduced absolute lymphocyte count, depressed CD4 (T-helper) lymphocyte count, or decreased CD4/CD8 (helper/suppressor) ratio, as long as subsequent antibody tests (e.g., Western blot, immunofluorescence assay), if done, are positive; OR
- c. a positive test for HIV serum antigen; OR
- d. a positive HIV culture confirmed by both reverse transcriptase detection and a specific HIV-antigen test or in situ hybridization using a nucleic acid probe; OR
- e. a positive result on any other highly specific test for HIV (e.g., nucleic acid probe of peripheral blood lymphocytes).

2. Against Infection:

A nonreactive screening test for serum antibody to HIV (e.g., ELISA) without a reactive or positive result on any other test for HIV infection (e.g., antibody, antigen, culture), if done.

3. Inconclusive (Neither For nor Against Infection):

- a. a repeatedly reactive screening test for serum antibody to HIV (e.g., ELISA) followed by a negative or inconclusive supplemental test (e.g., Western blot, immunofluorescence assay) without a positive HIV culture or serum antigen test, if done; OR
- b. a serum specimen from a child < 15 months of age, whose mother is thought to have had HIV infection during the child's perinatal period, that is repeatedly reactive for HIV antibody by a screening test, even if positive by a supplemental test, without additional evidence for immunodeficiency as described above (in 1.b) and without a positive HIV culture or serum antigen test, if done.

APPENDIX II

Definitive Diagnostic Methods for Diseases Indicative of AIDS

Diseases	Definitive Diagnostic Methods
cryptosporidiosis	microscopy (histology or cytology).
cytomegalovirus	
isosporiasis	
Kaposi's sarcoma	
lymphoma	
lymphoid pneumonia	
or hyperplasia	
<i>Pneumocystis carinii</i>	
pneumonia	
progressive multifocal	gross inspection by endoscopy or autopsy or by
leukoencephalopathy	
toxoplasmosis	microscopy (histology or cytology) on a specimen
candidiasis	obtained directly from the tissues affected (in-
	cluding scrapings from the mucosal surface), not
	from a culture.
coccidioidomycosis	microscopy (histology or cytology), culture, or
cryptococcosis	
herpes simplex virus	
histoplasmosis	
tuberculosis	detection of antigen in a specimen obtained
other mycobacteriosis	
salmonellosis	
other bacterial	
infection	culture.

HIV encephalopathy*
(dementia)

clinical findings of disabling cognitive and/or motor dysfunction interfering with occupation or activities of daily living, or loss of behavioral developmental milestones affecting a child, progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection that could explain the findings. Methods to rule out such concurrent illnesses and conditions must include cerebrospinal fluid examination and either brain imaging (computed tomography or magnetic resonance) or autopsy.

HIV wasting syndrome*

findings of profound involuntary weight loss >10% of baseline body weight plus either chronic diarrhea (at least two loose stools per day for > 30 days) or chronic weakness and documented fever (for > 30 days, intermittent or constant) in the absence of a concurrent illness or condition other than HIV infection that could explain the findings (e.g., cancer, tuberculosis, cryptosporidiosis, or other specific enteritis).

*For HIV encephalopathy and HIV wasting syndrome, the methods of diagnosis described here are not truly definitive, but are sufficiently rigorous for surveillance purposes.

APPENDIX II

Definition of encephalopathy in children with HIV-1 infection

Progressive encephalopathy is defined by 2 or more of the following with no explanation.

1. Impaired head growth documented by serial head circumference measurements over at least 3 months demonstrating acquired microcephaly or serial CT scans at least 3 months apart showing advancing cerebral atrophy.
2. A loss of developmental milestones or intellectual ability as determined on formal age appropriate neurodevelopmental testing instruments. These tests need to show a consistent pattern over at least 3 months.
3. Progressive motor deficit. This includes deterioration in gait, weakness, abnormalities in motor tone, or pathological reflexes which appear against a background of previously normal findings and/or persist at least 3 months.
4. CSF HIV-1 antigen determination with levels greater than 25 pg/ml. A negative finding cannot exclude the definition of progressive encephalopathy but a positive test strongly supports this diagnosis.

APPENDIX III

Suggested Guidelines for Presumptive Diagnosis
of Diseases Indicative of AIDS

Diseases	Presumptive Diagnostic Criteria
candidiasis of esophagus	a. recent onset of retrosternal pain on swallowing; AND b. oral candidiasis diagnosed by the gross appearance of white patches or plaques on an erythematous base or by the microscopic appearance of fungal mycelial filaments in an uncultured specimen scraped from the oral mucosa.
cytomegalovirus retinitis	a characteristic appearance on serial ophthalmoscopic examinations (e.g., discrete patches of retinal whitening with distinct borders, spreading in a centrifugal manner, following blood vessels, progressing over several months, frequently associated with retinal vasculitis, hemorrhage, and necrosis). Resolution of active disease leaves retinal scarring and atrophy with retinal pigment epithelial mottling.
mycobacteriosis	microscopy of a specimen from stool or normally sterile body fluids or tissue from a site other than lungs, skin, or cervical or hilar lymph nodes, showing acid-fast bacilli of a species not identified by culture.
Kaposi's sarcoma	a characteristic gross appearance of an erythematous or violaceous plaque-like lesion on skin or mucous membrane. (Note: Presumptive diagnosis of Kaposi's sarcoma should not be made by clinicians who have seen few cases of it.)
lymphoid interstitial pneumonia	bilateral reticulonodular interstitial pulmonary infiltrates present on chest X ray for ≥ 2 months with no pathogen identified and no response to antibiotic treatment.
<i>Pneumocystis</i> <i>carinii</i> pneumonia	a. a history of dyspnea on exertion or nonproductive cough of recent onset (within the past 3 months); AND b. chest X-ray evidence of diffuse bilateral interstitial infiltrates or gallium scan evidence of diffuse bilateral pulmonary disease; AND c. arterial blood gas analysis showing an arterial pO_2 of < 70 mm Hg or a low respiratory diffusing capacity ($< 80\%$ of predicted values) or an increase in the alveolar-arterial oxygen tension gradient; AND d. no evidence of a bacterial pneumonia.

toxoplasmosis
of the brain

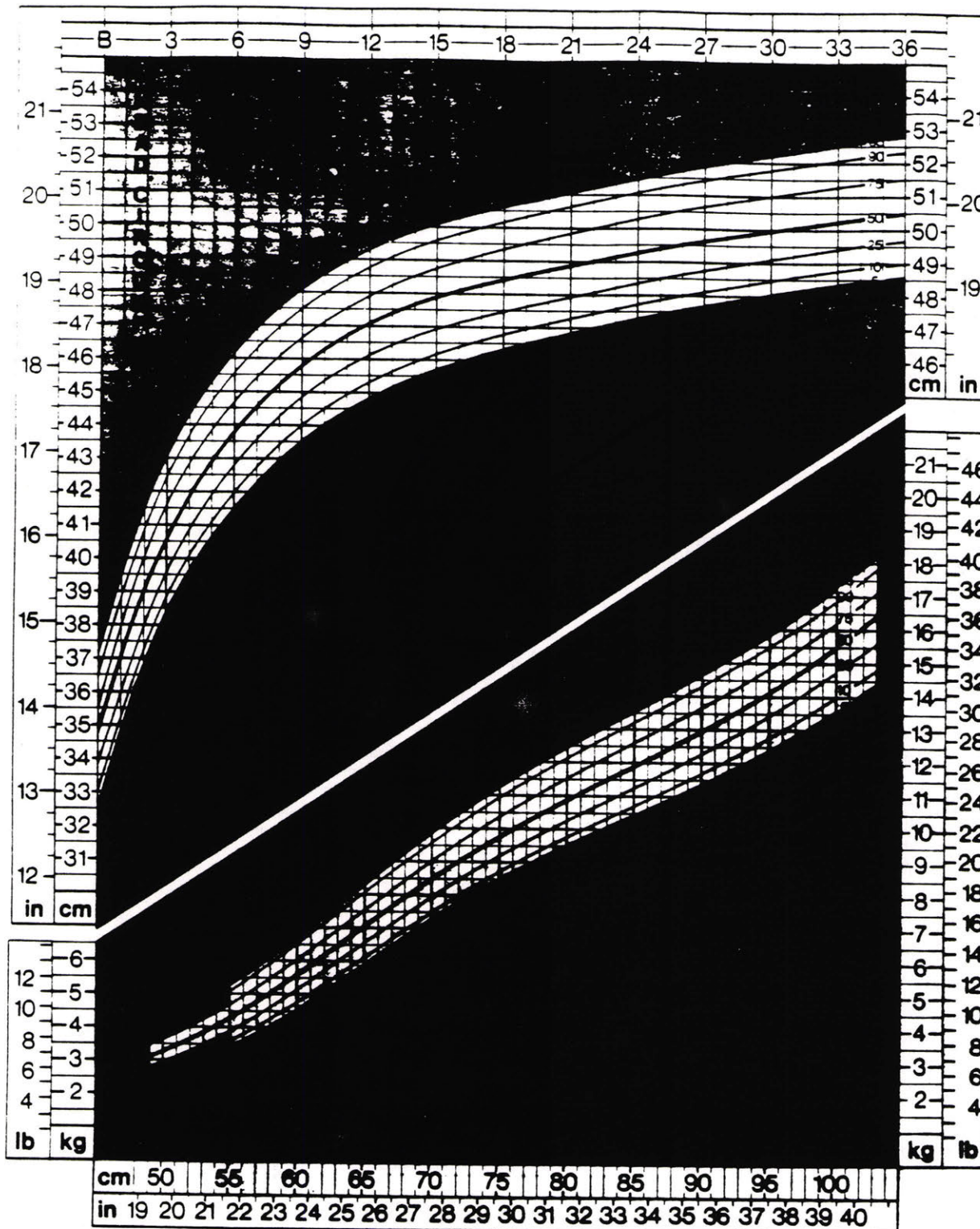
- a. recent onset of a focal neurologic abnormality consistent with intracranial disease or a reduced level of consciousness; AND
- b. brain imaging evidence of a lesion having a mass effect (on computed tomography or nuclear magnetic resonance) or the radiographic appearance of which is enhanced by injection of contrast medium; AND
- c. serum antibody to toxoplasmosis or successful response to therapy for toxoplasmosis.

**BOYS: BIRTH TO 36 MONTHS
PHYSICAL GROWTH
NCHS PERCENTILES***

APPENDIX III

NAME _____

RECORD # _____



*Adapted from: Hamill PVV, Drizd TA, Johnson CL, Reed RB, Roche AF, Moore WM. Physical growth. National Center for Health Statistics percentiles. AM J CLIN NUTR 32:607-629, 1979. Data from the Fels Research Institute, Wright State University School of Medicine, Yellow Springs, Ohio.

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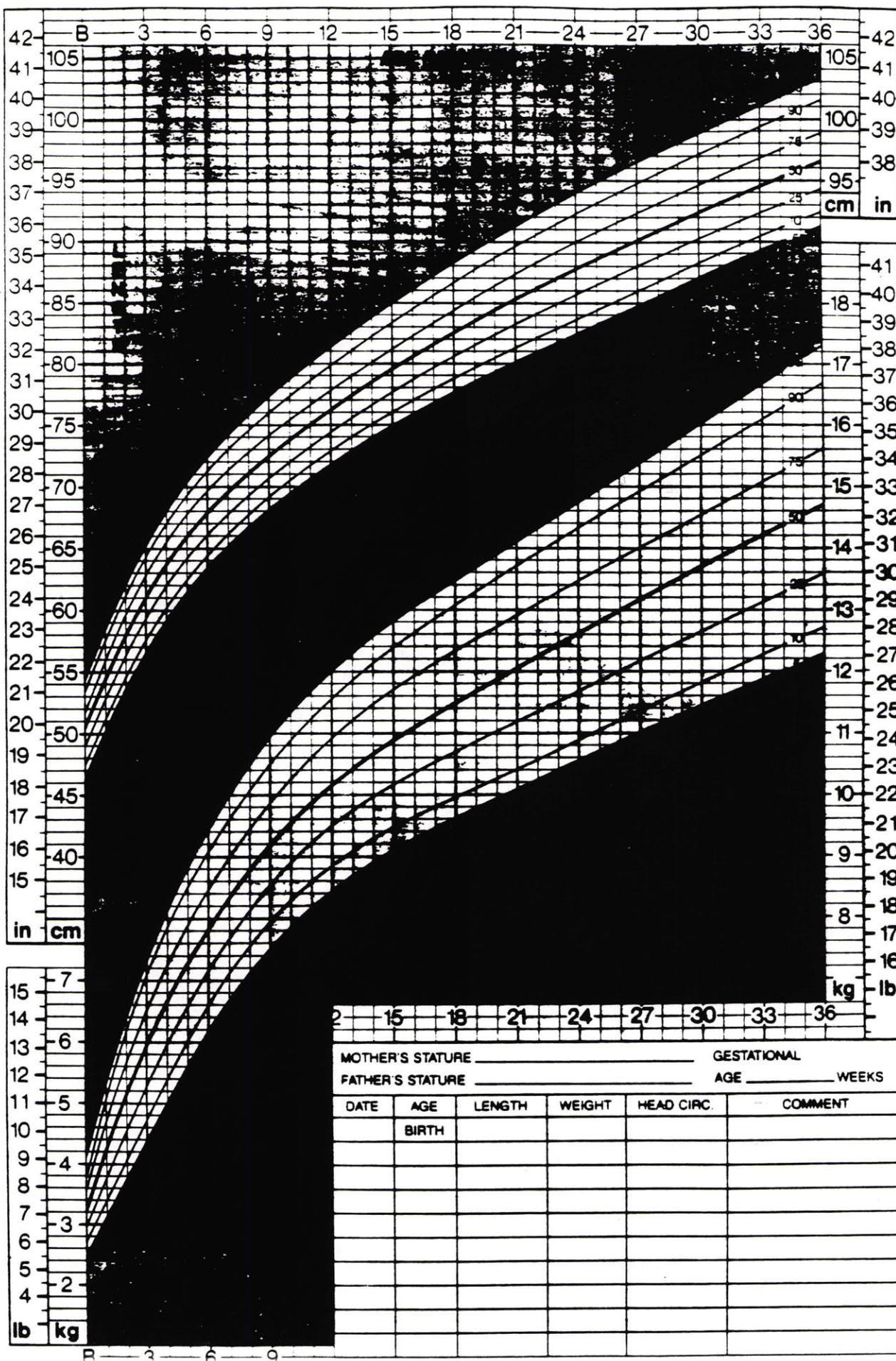
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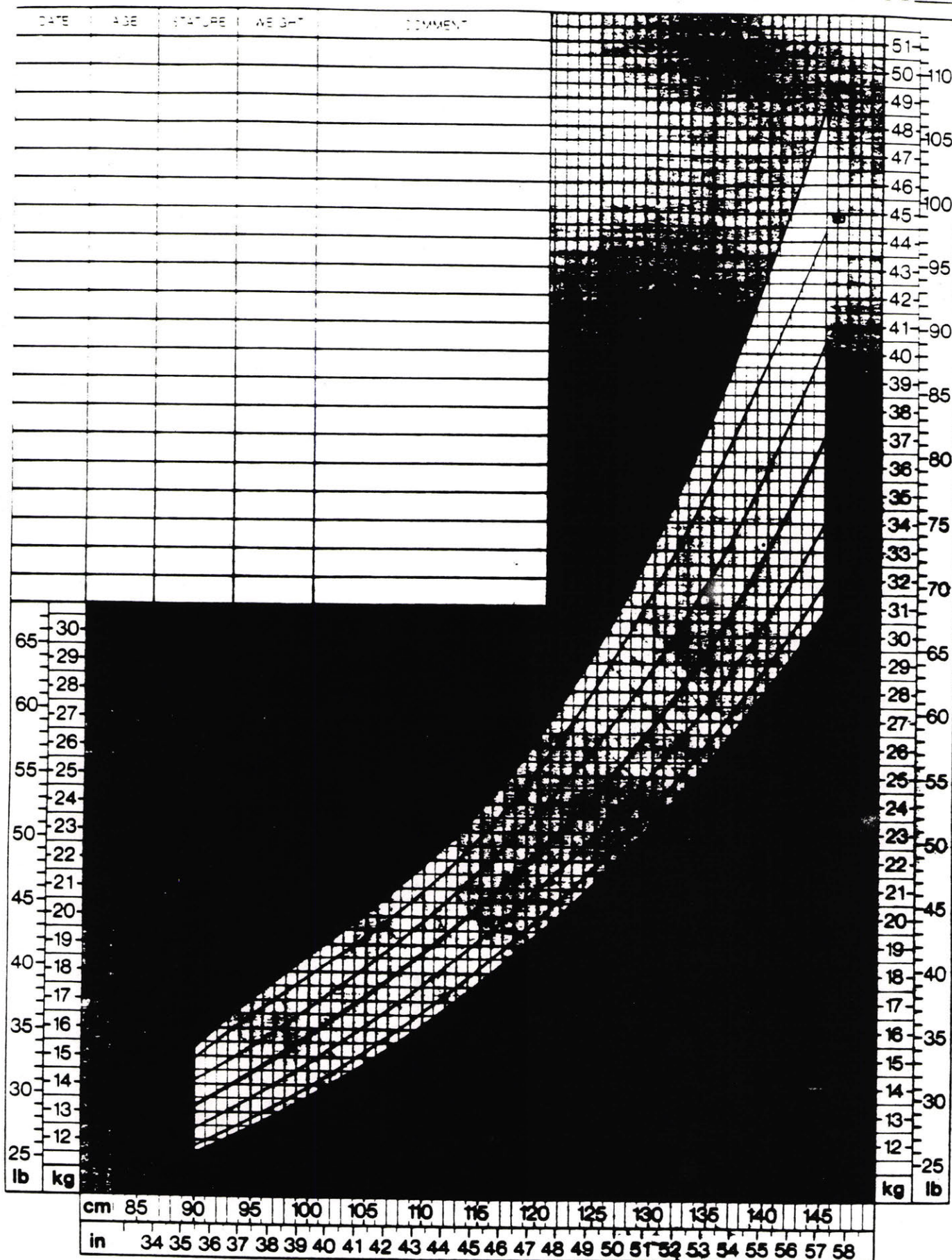
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Adapted from: Hamill PVV, Drizd TA, Johnson CL, Reed RB, Roche AF, Moore WM. Physical growth. National Center for Health Statistics percentiles. AM J CLIN NUTR 32 607-629, 1979. Data from the National Center for Health Statistics (NCHS), Hyattsville, Maryland.

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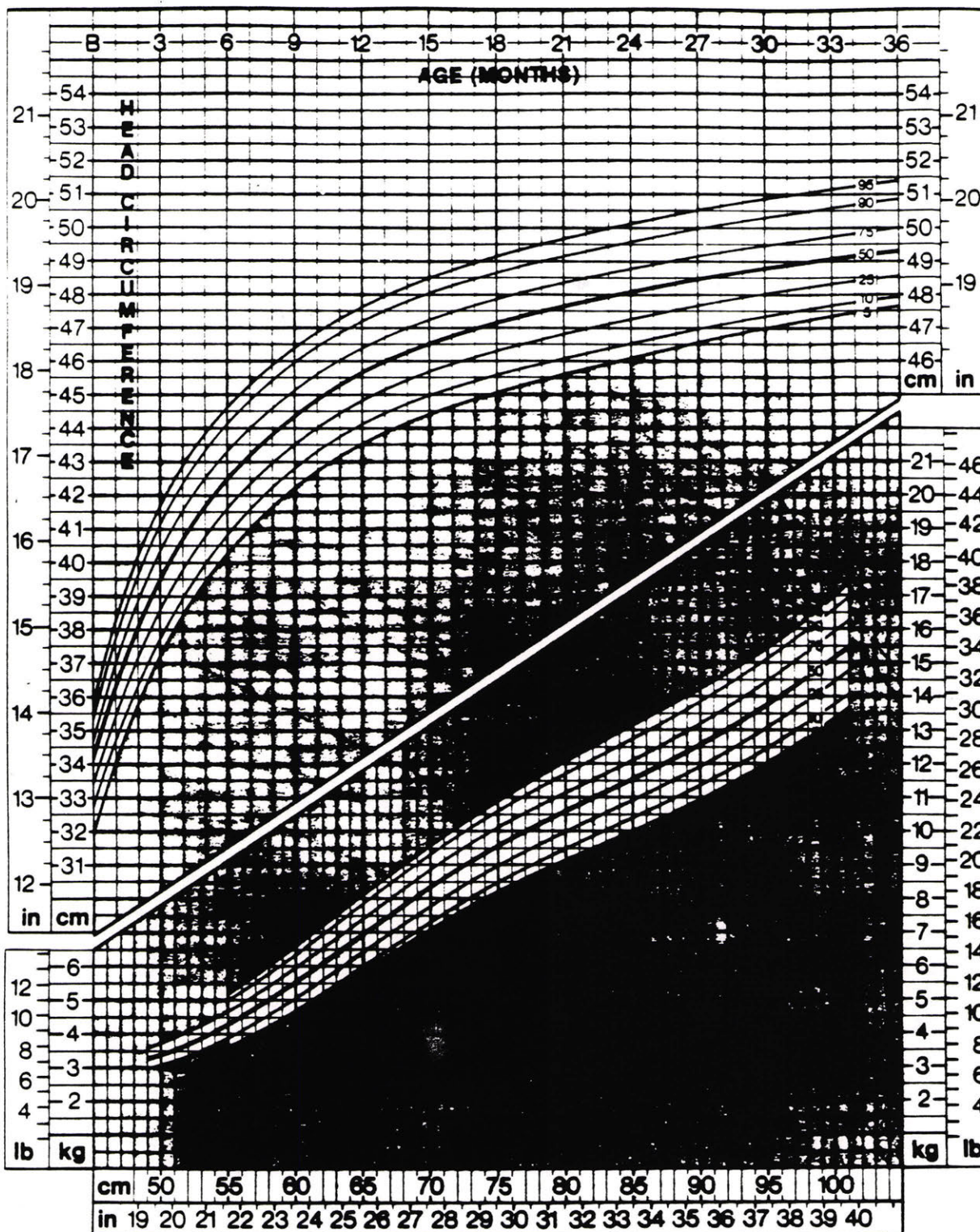
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GIRLS: BIRTH TO 36 MONTHS PHYSICAL GROWTH NCHS PERCENTILES*

APPENDIX III

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*Adapted from: Hamill PVV, Drizd TA, Johnson CL, Reed RB, Roche AF, Moore WM. Physical growth: National Center for Health Statistics percentiles. AM J CLIN NUTR 32:607-629, 1979. Data from the Fels Research Institute, Wright State University School of Medicine, Yellow Springs, Ohio.
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	BIRTH			

DATE	AGE	LENGTH	WEIGHT	HEAD C.

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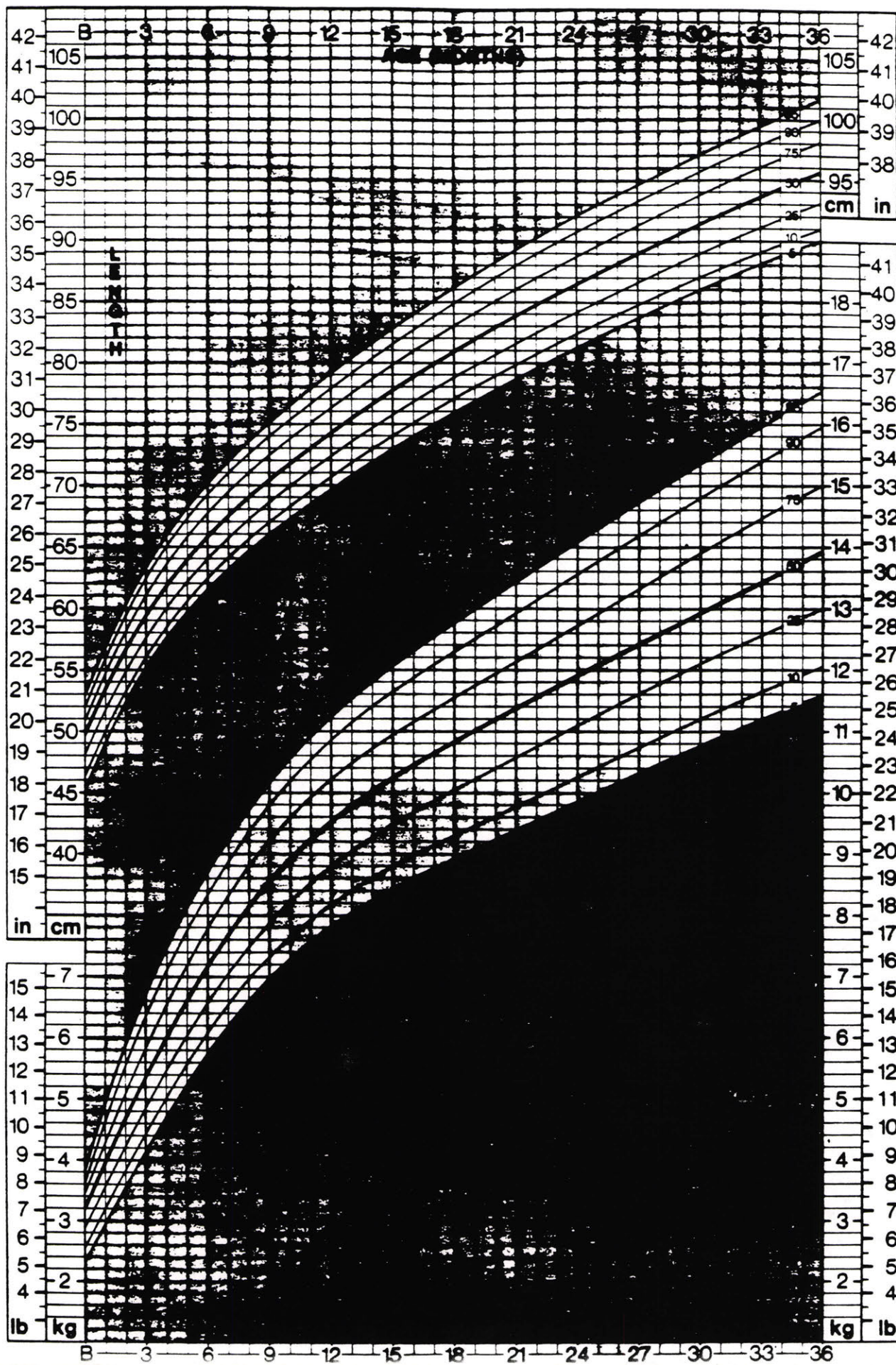
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**GIRLS: BIRTH TO 36 MONTHS
PHYSICAL GROWTH
NCHS PERCENTILES***

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APPENDIX III

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RECORD #

The image displays a medical chart template and a growth chart. The top section is a blank form with columns for 'MOTHER'S STATURE', 'FATHER'S STATURE', 'DATE', 'AGE', 'STATURE', 'WEIGHT', and 'COMMENT'. The bottom section is a growth chart with a grid showing percentile curves for height and weight from age 2 to 18. The left side of the growth chart has height in cm (62-29) and weight in kg (40-30). The right side has height in inches (210-60) and weight in pounds (100-30).

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APPENDIX ---

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APPENDIX IV

Instructions for Parents/Guardians

1. Zidovudine should be administered exactly as prescribed. Do not exceed the prescribed dose or share medication with anyone else.
2. Zidovudine should be administered either one-half hour before a meal or at least one hour after a meal.
3. Other medications, such as acetaminophen (Tylenol), may increase the side effects of zidovudine and should not be administered without consulting the Medical staff.
4. Report any side effects or change in your child's behavior that you think may be due to zidovudine.
5. Keep all scheduled appointments with the study center medical staff.
6. Return all used and unused vials to the medical staff at each visit.

^{TIL}
APPENDIX ~~III~~ - CLINICAL EVALUATION ~~AES~~

(Pre-entry = within 21 days of entry (start of medication))

	Pre-entry	Entry	1	2	3	4	6	8	10	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100
Physical Exam/Neuro Exam	X	X						X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight & Vital Signs	X	X ⁺	X	X	X	X	X	X ⁺	X	X	X ⁺	X	X ⁺	X	X ⁺	X	X ⁺	X	X ⁺	X	X ⁺	X	X ⁺	X	X ⁺	X	X ⁺	X	X ⁺	X	X ⁺	X
HIV-Associated Symptoms	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Neuropsychiatric Testing ^S	X										X		X				X				X						X					X
CT Scan of Brain ^S		X														X [*]													X [*]			
CXR		X ¹																		X												X
Lumbar Puncture ^S	X ²	(Pre-entry CSF and serum for culture and p24 antigen should be obtained on the same day.)																														
EKG		X																		X ^{**}												X ^{**}
Echocardiogram ^S		X																		X ^{**}												X ^{**}

* Obtain if entry scan was abnormal

** Cardiomyopathy only; obtain additional exams as clinically indicated

X¹ Children with concurrent LIP require CXR's at 12-week intervals

X² Repeat as clinically indicated

^S Selected sites only (refer to 11,10)

+ recalculate body surface area (m²) and weight every 8 weeks (refer to 7.25)

IV
APPENDIX - LABORATORY EVALUATION

ABG 01

(Pre-entry = within 21 days of entry (start of medication))

			WEEK																																		
	Pre-entry	Entry	1	2	3	4	6	8	10	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100					
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Chemistries, Urinalysis (dipstick)	X	X				X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
CPK ¹	X	X					X				X		X		X		X		X		X		X		X		X		X		X		X				
T4 + T8 lymphocytes	X	X ²				X				X				X				X				X				X							X				
Virology - (serum HIV culture)	X	X				X				X				X				X				X				X							X				
Virology - (Serum p24 antigen)	X	X				X				X				X				X				X				X							X				
Immunoglobulins	X	X									X**				X**				X**							X**								X**			
ABG ⁺																																					
O ₂ saturation*	X	X				X*	X*			X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*				
Serum for storage (q 3 months)		X								X			X			X			X			X			X			X					X				
Pregnancy Test as indicated	X																																				

¹ Isoenzymes will be obtained at the same time as CPKs in children with evidence of clinical myositis

² A second CD4+ determination will be obtained at entry in order to establish patient's baseline

** Obtain prior to administration of IVIG/placebo

+ Children with only LIP as an entry criteria, must have a documented PaO₂ < 70 mmHg at some point in their pre-enrollment clinical record

* Every month as indicated for children with cardiac or pulmonary dysfunction (obtained via oximetry)

RECOMMENDATIONS FOR GRADING OF ACUTE AND SUBACUTE TOXIC EFFECTS (children)

Parameter	0 (None)	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life-threatening)
Hematologic					
1. Hemoglobin (g/dl) < 2 yr.	≥ 10.0	9.0-9.9	7.0-8.9	< 7.0	Failure 2 ^o anemia
> 2 yr.	≥ 11.0	9.9-10.9			
2. Leukocytes (x10 ³ /mm ³)	≥ 4.0	3.0-3.9	2.0-2.9	1.0-1.9	< 1.0
3. Neutrophils + bands (total count/mm ³)				< 1000	< 500
4. Platelets/cmm	≥ 100,000	75,000-99,999	50,000-74,999	25,000-49,999	< 25,000
5. MCV (cubic microns)	80-94			100-115	> 115
Gastrointestinal					
1. Bilirubin (total)	< 1.0 x N ¹	1.0-1.4 x N	1.5-1.9 x N	2.0-4.9 x N	≥ 5.0 x N
2. SGOT	< 1.0 x N	1.0-1.9 x N	2.0-4.9 x N	5.0-9.9 x N	≥ 10.0 x N
3. Alkaline Phosphatase	< 1.0 x N	1.0-1.4 x N	1.5-1.9 x N	2.0-4.9 x N	≥ 5.0 x N
4. Abdominal Pain	none	mild - no treatment	moderate - no treatment	moderate - requires Rx	severe - Hosp. + Rx
5. Diarrhea	none	soft stools	increased no. of liquid stools	liquid stools - dehydration	IV therapy required
6. Nausea and Vomiting	none	nausea only	transient vomiting	vomiting > 3x day/ dehydrated	intractable vomiting IV rehydration
Allergic					
	none	transient rash; fever ≤ 38.5°C	diffuse rash or urticaria temp > 38.5°C	bronchospasm - parenteral therapy required; fever > 40°C	anaphylaxis

¹N=upper limit of normal

TOXICITY SCALE FOR CHILDREN

Parameter	0 (None)	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life-threatening)
Cutaneous	none	transient erythema; local maculo-pap rash	dry desquamation, vesiculation, pruritus, persistent erythema	moist desquamation, ulceration	exfoliative dermatitis, necrosis requiring surg, intervention
Renal					
1. BUN	< 20	20-39	40-59	60-79	≥ 80
2. Creatinine	≤ 1.2	1.3-1.9	2.0-3.9	4.0-5.9	≥ 6.0
Serum Electrolytes					
1. Sodium (meq/L) increased or decreased	135-144	145-149 130-134	150-154 125-129	155-164 115-124	≥ 165 < 115
2. Potassium (meq/L) increased or decreased	3.5-5.4	5.5-5.9 3.0-3.4	6.0-6.4 2.5-2.9	6.5-6.9 2.0-2.4	≥ 7.0 < 2.0
3. Calcium (mg/dl) increased or decreased	8.5-10.4	10.5-11.2 7.8-8.4	11.3-11.9 7.0-7.7	12.0-12.9 6.0-6.9	≥ 13.0 < 6.0
Neurologic					
1. Peripheral - muscular sensory Autonomic	normal normal normal	DTR mild parathesia normal	absent DTR severe parathesia normal	Severe weakness sensory loss obstipation and bladder dysfunction	Paralysis
2. Central	normal	mild lethargy, headache - no therapy required, irritability	obtunded, confusion ataxia, slurred speech HA requiring analgesic	seizures, delerium somnolent > 50% of waking hours HA requiring narcotic	comatose
¹ Upper limit of normal					

APPENDIX VII

Neuropsychological Assessment

Neuropsychiatric evaluations will be conducted by a qualified psychologist prior to entry (within 14 days of entry), and at weeks 12, 24, 40, 56, 80 and 100. The children will serve as their own controls.

Neuropsychiatric testing will consist of the following evaluations:

1) Children 3 through 30 months of age⁺:

Pre-entry * Bayley Scales of Infant Development
(1969 version)

Week 12 * Bayley Scales of Infant Development

Week 24 * Bayley Scales of Infant Development

Week 40 * Bayley Scales of Infant Development

Week 56 * Bayley Scales of Infant Development

Week 80 * Bayley Scales of Infant Development

Week 100 * Bayley Scales of Infant Development

2) Children > 30 months through 5 years of age⁺:

Pre-entry * McCarthy Scales of Childrens' Abilities

* Peabody Picture Vocabulary Test (Form L)

* Beery Visual Organization Test

* Kaufman Assessment Battery Core (KABC) - Only Subtest
Memory Recall (Test #5)

Week 12 * Peabody Picture Vocabulary Test (Form L)

* Beery Visual Organization Test

* KABC - Only Subtest Memory Recall (Test #5)

⁺(Refer to Section 11.3 in protocol ACTG #051).

Week 24 * McCarthy Scales of Childrens' Abilities
* Peabody Picture Vocabulary Test (Form L)
* Beery Visual Organization Test
* KABC - Only Subtest Memory Recall (Test #5)

Week 40 * Peabody Picture Vocabulary Test (Form L)
* Beery Visual Organization Test
* KABC - Only Subtest Memory Recall (Test #5)

Week 56 * McCarthy Scales of Childrens' Abilities
* Peabody Picture Vocabulary Test (Form L)
* Beery Visual Organization Test
* KABC - Only Subtest Memory Recall (Test #5)

Week 80 * McCarthy Scales of Childrens' Abilities
* Peabody Picture Vocabulary Test (Form L)
* Beery Visual Organization Test
* KABC - Only Subtest Memory Recall (Test #5)

Week 100 * McCarthy Scales of Childrens' Abilities
* Peabody Picture Vocabulary Test (Form L)
* Beery Visual Organization Test
* KABC - Only Subtest Memory Recall (Test #5)

3) Children 6 through 12 years of age[†]:

Pre-entry * Wechsler Intelligence Scale for Children (WISC-R),
Revised (1974 version).
* Peabody Picture Vocabulary Test (Form L)
* Beery Visual Organization Test
* Digit Span Subtest Only - From WISC-R (1974 version)

[†](Refer to Section 11.3 in protocol ACTG #051).

- Week 12 * Peabody Picture Vocabulary Test (Form L)
* Beery Visual Organization Test
* Digit Span Subtest Only - From WISC-R (1974 version)
- Week 24 * WISC-R, Revised (1974 version).
* Peabody Picture Vocabulary Test (Form L)
* Beery Visual Organization Test
* Digit Span Subtest Only - from WISC-R (1974 version)
- Week 40 * Peabody Picture Vocabulary Test (Form L)
* Beery Visual Organization Test
* Digit Span Subtest Only - from WISC-R (1974 version)
- Week 56 * WISC-R, Revised (1974 version)
* Peabody Picture Vocabulary Test (Form L)
* Beery Visual Organization Test
* Digit Span Subtest Only - from WISC-R (1974 version)
- Week 80 * WISC-R, Revised (1974 version).
* Peabody Picture Vocabulary Test (Form L)
* Beery Visual Organization Test
* Digit Span Subtest Only - from WISC-R (1974 version)
- Week 100 * WISC-R, Revised (1974 version).
* Peabody Picture Vocabulary Test (Form L)
* Beery Visual Organization Test
* Digit Span Subtest Only - from WISC-R (1974 version)

Section 11.3 refers to **Appendix VII, the Neuropsychological Assessment**, which has been revised. Guidelines for appropriate test administration have also been added to section 11.3.

Section 11.92 has been revised to read:

"Concurrent medications, receipt of blood products, and adverse experiences will be recorded on a continuous basis (i.e., upon drug administration or occurrence of event). Prophylaxis for oral candidiasis, or chronic otitis media or other infections (sinusitis, UTI) is prohibited. Likewise, the administration of immunoglobulin therapy is prohibited except for single dose exposure prophylaxis. PCP prophylaxis as outlined in sections 7.42 and 7.43 is allowed. Medications and blood products administered within 4 weeks prior to entry should also be recorded."

Section 11.94 has been changed. This section now states:

"Isoenzyme evaluations will be obtained at the same time as CPK evaluations in children with clinical evidence of myositis."

Section 12.3 has been added to the protocol. This change can also be noted in Appendix VIII (Laboratory Schedule of Evaluations).

Pre-entry, entry, and every 8 weeks thereafter

CPK

Sections 12.4 through 12.11 have been renumbered accordingly.

Appendix VII - The Neuropsychological Assessment has been revised in order to obtain more effective information.

Appendix VIII - The Laboratory Schedule of Evaluations has been adjusted to reflect the addition of CPK evaluations.

Copies of protocol ACTG #051 dated 9/28/88 and labeled Version 2.0, were distributed at the 4th ACTG Meeting on October 7 in Bethesda, Maryland. These copies were distributed for the purpose of participation in the #051 start-up meeting and do not include the restructured toxicity section.

Please submit this protocol and the attached list of amendments to your IRB for review and approval. IRB approval and site registration must be completed with the AIDS Program in order to participate in this protocol. Elizabeth Moore located at the NIAID-AIDS Program (301) 496-8210, can assist you or answer questions regarding these requirements.

Please contact me at (301) 230-3150 if there are further questions regarding this protocol. Thank you for your patience.

PROTOCOL TEAM FOR ACTG #051

A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO EVALUATE INTRAVENOUS GAMMA GLOBULIN IN CHILDREN WITH SYMPTOMATIC HIV INFECTION RECEIVING ZIDOVUDINE

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APPENDIX IX

Reporting of Adverse Experiences

Timely and accurate reporting of Adverse Experiences is required, not only for regulatory compliance, but to determine if unexpected toxicities have occurred or if the incidence or severity is greater than expected, and if necessary, to quickly disseminate information to investigators working with the drug. Each Adverse Experience Report submitted to the AIDS Program Office is reviewed and evaluated by the AIDS Program Medical Officers to determine the Adverse Experience's likely relation to the drug. Based on the medical assessment, a decision is made concerning the need for further action. The prime consideration is whether the new findings affect the safety of patients enrolled in ongoing studies. If so, the AIDS Program Office takes immediate steps to notify the investigator community and the FDA.

The identification and definition of an adverse experience, as it relates to the drug treatment, presents special problems for the investigator and sponsor because many patients develop symptoms related to HIV virus infection and its associated complications. The centralization of information on suspected Adverse Experiences makes possible a much more accurate determination of the degree to which a suspected reaction is in fact drug-related. Monitoring toxicities from a multicenter perspective provides the opportunity to identify toxicities which may occur in a smaller percent of the population and which may range widely in severity.

1. The prompt reporting of adverse experiences to the AIDS Program Office is the responsibility of each investigator. Investigators are encouraged to submit reports even if there is a possibility of a drug effect.
2. All deaths must be reported to the AIDS Program Office.

3. For patients off drug:
 - a. report deaths which occur within three months;
 - b. other adverse experiences/toxicities which occur within 30 days and meet the reporting requirements as noted on the next page.
4. The need for a change in dosage is NOT appropriate criteria in making the decision of whether to report an adverse experience. Please report those adverse experiences which do not require a dose change, but may possibly be related to drug use.
5. Progression of disease which is DEFINITELY NOT related to drug treatment, is not an adverse experience and should not be reported on AER forms.
6. In addition to the required AER Form, the routine, required CTCC Case report forms should be completed, whether the toxicity is noted during a routine scheduled visit or as a part of an unscheduled visit.
7. Adverse experiences should also be reported to your local Institutional Review Board.
8. Investigators may be asked to provide additional information if necessary. Continued failure to report in a timely and accurate manner or failure to supply information requested regarding particular adverse experiences may result in suspension of the investigator's clinical research with the AIDS Program Office.

REPORTING REQUIREMENTS

Phase I/Pediatric Studies - Adverse Experience Reporting Requirements

Expected	Grades 3 & 4	send AER form within five days
	Grade 5	deaths and immediately life-threatening event which could possibly be related to drug use - phone 1-800-537-9979 within 24 hours, send AER form within three days
Unexpected	Grades 2 - 4	send AER form within five days
	Grade 5	deaths and immediately life-threatening events which could possibly be related to drug use - phone 1-800-537-9979 within 24 hours, send AER form within three days.

Mail AER Forms to: Adverse Experience Report Office
 Treatment Branch, AIDS Program, NIAID
 6005 Executive Boulevard
 Rockville, MD 20852

ZIDOVUDINE INTRAVENOUS FORMULATION FOR
ORAL ADMINISTRATION

FACTSHEET

1. Zidovudine intravenous formulation is supplied in 10 ml amber glass vials with a concentration of 20 mg of zidovudine per ml.
2. The vials must be stored at room temperature (59-86 F) and out of direct sunlight.
3. If solution is transferred to a substitute container, only a glass amber bottle may be utilized.
4. For oral dosing, the intravenous solution may be mixed with either water, orange juice, unpreserved apple juice, or apple sauce immediately prior to administration. Do not mix zidovudine with water or juice prior to the time of dosing.
5. It is preferable that oral dosing be administered either one-half hour prior to a meal/feeding or at least one hour after a meal/feeding.
6. There are no bacteriostatic additives or other preservatives in the zidovudine intravenous formulation.
7. Zidovudine is very stable in solution. Each lot of zidovudine injection is periodically submitted for stability testing. If any lot is found unstable, the drug will be recalled to Burroughs Wellcome Co. There is no "expiration" date on the vials.
8. Parents/guardians must demonstrate the ability to dispense the child's correct dose prior to receipt of the child's zidovudine supply.

IVIG, AND IV ALBUMIN ADMINISTRATION

Source of IVIG:	Cutter Biological, Miles, Inc.
Route of administration:	Intravenous
Storage:	Products contain no preservatives. Must be stored at 2-8°C until used.
Preparation:	Should be pooled into sterile bags or bottles under a sterile hood. Must be filtered in the pharmacy with a 5 micron filter prior to infusion. Infusion must start within one hour of pooling. Product is to be at room temperature for infusion.
Restrictions:	Frozen or heated products may not be used. Entered vials must be used immediately; do not retain for future use. Infusion may not start more than one hour after pooling.
Use with other IV fluids?	No -- use undiluted but piggyback to D5W in case infusion needs to be stopped; D5W flush only.
Use with other IV medications?	No
Dose:	8mL/kg body weight
Medications:	Not required, antihistamines and/or antipyretics may be administered prior to infusion in patients previously demonstrating mild reactions or during infusion if reaction occurs.
Dosing interval:	Every 28 $\pm$ 7 days for 2 years
Infusion rate:	0.01-0.02 mL/kg/min. x 15-30 min.; if no adverse effects, increase gradually to 0.02-0.04 mL/kg/min. If well tolerated, increase gradually to 0.04-0.06 mL/kg/min. If well tolerated, increase to maximum of 0.08 mL/kg/min. If no adverse effects in first two infusions received by a child, subsequent infusions may be started at a higher rate in that child. Do <u>not</u> exceed maximum rate.

Appendix XI

Monitoring (minimum requirements): Vital signs (P, BP, R, T) before beginning, at the midpoint of infusion, and at end of infusion. If adverse reaction, vital signs at time of reaction. If interruption, vital signs at time of interruption and thirty minutes later.

Record: Dosage;
Study number;
Vital signs;
Duration of infusion;
Adjustment of infusion rate, if necessary;
Other medication administered, if any, indication for meds; and
Adverse reactions, if any.

Reminder: Study bloods must be drawn before infusion starts.

CONSENT TO ACT AS A RESEARCH SUBJECT

Drs. _____ are conducting a study to evaluate the effectiveness of Zidovudine (AZT, Zidovudine), and intravenous gammaglobulin (IVIG) in the treatment of children with pediatric AIDS or with other clinical symptoms associated with human immunodeficiency virus (HIV) infection. Zidovudine is an experimental drug in children which interferes with the growth of HIV virus. It has been shown to prolong survival in adults with AIDS or with severe AIDS-related complex (ARC). Another name for antibodies is immunoglobulin. When given intravenously (by vein), it is called IVIG. IVIG is a licensed drug which has been shown to protect children who don't make antibodies from serious bacterial infections like blood infections and meningitis.

My child has been asked to take part in this study because he/she is infected with HIV and has either pediatric AIDS or symptoms associated with HIV infection. It is known that these children are at high risk to develop serious bacterial infections, but it is unknown if IVIG will help decrease these infections. If I agree to have my child participate in the study, my child will receive zidovudine for two years. The drug will be mixed with juice and my child will be asked to drink this solution every 6 hours (4 times daily). To tell whether IVIG actually does any good or not, it has to be compared with a drug which actually has no effect at all (this is called a placebo). Half the children in this study will receive immunoglobulin; the other half will receive the placebo. This will be decided by random selection (a process similar to flipping a coin) to see who receives IVIG and who receives the placebo. The children getting immunoglobulin will be compared with the children getting the placebo to see whether one group has fewer bacterial infections than the other. Whether your child is receiving the immunoglobulin or the placebo will not be known by you or your physician until the end of the study. This is very important to make sure that the study remains unbiased. All children will receive zidovudine (AZT) during this study.

I understand that my child will come to the clinic to be examined weekly for the first 4 weeks, every other week for the next two months and then monthly until the end of the study. I understand that my child will receive intravenous IVIG or intravenous albumin placebo once a month for two years. The treatment will take about four hours.

During the course of this study, your child will be watched carefully, both by your doctor and by a safety monitoring committee. The number and severity of infections in your child will be watched carefully.

A chest x-ray, electrocardiogram and echocardiogram (a heart examination using sound waves) and a computerized tomogram and/or magnetic resonance imaging (MRI) scan of the head will be performed before entering the study and at certain times during the study. Chest x-rays and CT scans

Appendix XII

require small amounts of radiation exposure which are within accepted limits of standard diagnostic tests. There are no additional known risks of these procedures.

The major side effect of zidovudine is a decrease of red blood cells (anemia) which may require blood transfusions. A lower white blood cell count has also been reported that might further predispose my child to other infections. Other side effects reported in adults include anxiety, nausea, skin rashes, headaches and itching. Generally, these effects occur after 6 weeks of treatment and usually go away when the drug is discontinued. Long term side effects are not known at this time but may possibly include tumors and birth defects.

The major side effects associated with IVIG are flushing, chills, back pain, muscle aches, nausea and fever. Less commonly, it can cause a sensation of chest tightness, shortness of breath or low blood pressure. These side effects do not happen often and usually go away when IVIG is given more slowly. A serious allergic reaction is a rare possibility. In general immunoglobulin is a safe drug with few serious side effects. It is possible that the treatment with IVIG may involve risks that are not foreseeable at this time.

Blood (1-3 teaspoons) will be drawn from my child before therapy begins, weekly for the first 4 weeks, biweekly for the next 8 weeks and then every 4 weeks during the course of treatment to assess for any toxicity or improvement associated with treatment and to determine the virologic response. Drawing blood from the vein or having an I.V. includes some risks including some pain at the puncture site, and less commonly, there may be the formation of a small clot or swelling of the surrounding tissue, bleeding from the puncture site or infection.

Your child will have cerebrospinal fluid collected by lumbar puncture prior to starting treatment and two additional times during the study. To collect a sample, a spinal needle will be inserted into the lower back and into the fluid surrounding the spinal cord. Samples are collected by withdrawing fluid through the needle. A numbing medicine may be used to reduce the pain caused by the needle. Your child may experience a headache or discomfort at the needle site following the procedure. Other risks of a lumbar puncture include nerve damage and infection; however, they are very very rare.

I understand that there is no evidence that zidovudine or IVIG are a cure for AIDS or HIV infection, but current data suggests that they may prolong life for some individuals who have AIDS or severe ARC. It is possible my child may derive no benefit from participation in this investigation.

I understand that my child's treatment will be provided completely free of charge for the duration of this study. I will not have to pay for the clinic or hospital costs during each monthly four-hour treatment for my child. All other medical costs outside this study, however, will be paid in the usual manner. I understand that I will receive no money for my child's participation in this study.

I understand that immediate necessary care is available if a patient is injured because of participation in a medical study. However, free medical care or monetary compensation for such injury is not provided. I may call (619) 534-4520 for more information about this or to report research problems, or you can contact the Hospital Risk Management Office.

If my child is a female and capable of child bearing, a sample of urine will be collected before the study is begun in order to be as sure as possible that she is not pregnant. Girls who are sexually active must use contraception methods (such as abstinence, diaphragm, condom, or intrauterine device) to prevent pregnancy for the duration of the study as the drug being tested might cause harm to an unborn child.

Dr. _____ has explained this study to me and answered my questions. If I have other questions or research-related problems, I may reach Dr. Spector at (619) 543-6447.

Participation in research is entirely voluntary. I or my child may refuse to participate or withdraw at any time without jeopardy to the medical care he/she will receive at this institution. At this time, no alternative treatment of my child's basic disease has been shown to be curative. I can choose to have my child have no therapy for his/her infection.

Research records will be kept completely confidential. Study forms will contain only a code number and not my child's name for identification. Study records may be reviewed by the AIDS Clinical Trial Coordinating Center, the NIAID, the Burroughs Wellcome Company, Cutter Laboratories, or the Food and Drug Administration, to assure that they are accurate and fulfill federal regulations.

I have received a copy of this consent document and "The Experimental Subject's Bill of Rights."

Parent's or Guardian's Signature Date

Subject's Signature

Witness' Signature

Minor

CONSENT TO ACT AS A RESEARCH SUBJECT

Drs. _____ are doing a study to find out whether two new medicines called zidovudine (AZT, Retrovir) or intravenous gammaglobulin (IVIG) is useful for treating children with AIDS or who have symptoms associated with infection with HIV (the virus that causes AIDS). They have asked me to take part in this study because I have pediatric AIDS or because I have had symptoms associated with my infection with HIV.

If I agree to be in the study, I will have medicine given in my vein once a month, samples of blood drawn from my arm and will have spinal taps during the study. I will also have tests of my heart and x-rays of my lungs and head during the study.

The blood sampling and spinal tap may hurt, and a bruise may form where the needle enters. I also may have a headache after the spinal tap.

Dr. Spector or one of his helpers has explained this study to me. If I have any more questions, he will answer them.

I agree to be in this study.

Subject's Signature

Date

PROTOCOL TEAM FOR ACTG #051

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On behalf of Project Inform, I would like to state our organization's opposition, as well as my personal opposition, to the proposed placebo-controlled study of intravenous gamma globulin.

The fault here is not that some patients will receive no treatment, as AZT will be administered to all patients. The fault lies in the investigators' rigid insistence upon matching the children treated with IV gamma globulin with a group of controls who, despite being subjected to severe discomfort and the risk of infection associated with IV infusion, will receive only an inert placebo. After thorough consideration, we find this unconscionable.

There is nothing in the medical literature to suggest that infants and small children are affected by the psychological trick of placebo use. Thus, the use of placebos in this study can only be justified for two possible reasons: (1) to make sure that both treated children and placebo controls are exposed to equal risk of staph infection associated with IV infusion, or (2) that physicians do not unintentionally provide preferential treatment to one group or the other. Neither of these reasons are provide moral justification for the pain inflicted on the children, nor are the reasons medically compelling.

We do not question the need for a conclusive finding on the value of IV gamma globulin. However, we firmly believe that the only design of this study which meets ethical and moral requirements would be the use of randomized untreated controls, rather than randomized placebo-treated controls. While some might argue that this is medically less precise, we feel any scientific compromise it represents is far outweighed by the moral and humane benefits it provides.

Finally, we must express our distress at the University of California IRB which approved the design of this study. We feel the appropriate balance of human and scientific concerns has been violated here and urge immediate reconsideration of the study or a recall of the IRB itself.

As a member of the Mayor's HIV Task Force and the National Academy of Sciences Roundtable on the Development of Drugs and Vaccines for AIDS, I feel compelled to bring this issue to the attention of each of the committees on which I serve.

Martin Delaney

Martin Delaney
Co-Executive Director, Project Inform

Placebo controls -
- AZT phase II
- 019
- 016

** or in person
fwd. 4/51*

]

ivig2

6/14/89

To: Participants at the June 17th meeting with Act Up and UCSF
 From: Michelle Roland, member Act Up Treatment Issues Committee
 Date: June 17, 1989

Some further elucidation of the points raised in the letter from Hank Wilson, dated 6/13/89

1. Use of a placebo in children facing a life-threatening disease.

A. Is it ethical, in the context of a life-threatening disease, to withhold **potentially effective** treatments from people with the disease if they want to try it, aware that it has not been proven effective and has some toxicity associated with it?

B. If a parent wanted access to IVIG and was not willing to take the risk of receiving the placebo instead of the IVIG, would the physician prescribe IVIG for the patient, even if the child was eligible for the trial? If not, because of the existence of the clinical trial, then parents are essentially forced into entering the trial if they want their children to have some chance of receiving the treatment. The argument may be given that it would be impossible to enroll people in clinical trials with placebos if this option was left open (of course, this case is unusual because the drug is currently approved). My argument in response to this argument is that clinical trials must be designed so they meet the needs of individual subject/patients. If they meet these needs by offering the treatment to all participants who want it, there won't be a problem getting people to enter clinical trials

2. Use of a placebo when non-placebo alternative exist.

A. We are aware that the double blind placebo controlled trial is the gold standard in American research. We are also aware that alternatives exist and that there is significant controversy about the efficacy of placebo controlled RCTs, natural history controls, standard treatment controls, etc. We are aware that the alternatives we present are not ideal, however we think the benefits of non-placebo controlled trials outweigh the risks and we challenge the medical and scientific communities to work with people with HIV infection and their advocates to design ethical and scientifically sound trials.

B. In the specific case of IVIG, we offer the following alternatives:

1. Historical controls. Look at average numbers and types of infections, life span, etc. in children who have not received the treatment and compare these factors to children who are being treated. Pick your controls carefully so that comparisons can be made validly.

2. Current no treatment or alternative treatment (e.g. AZT) controls. The important distinction here is that people be given the choice of which, if any, treatment they want to use. Some people will choose not to try an experimental treatment, or one, like IVIG, that has some significant risks and discomfort

associated with it. The arguments immediately arise about selection bias and reporting bias. Devise methods to minimize the reporting bias by what types of markers are compared. Devise methods to identify any significant selection biases and control for them in data analysis.

3. Use of IV placebo with potential for infection in children who may already be immune suppressed.

A. It seems unconscionable to expose immune suppressed children to increased risk of infection by giving them an IV placebo. Two arguments have been put forth. the first is that any local infections caused by the administration of IVIG must be controlled for in order to determine the safety and efficacy of the drug itself. My argument is that the method of administration is, in a case like this, part of what needs to be examined for safety. If you control out local infections, that important information is lost in trying to weigh the risks and benefits of the treatment.

B. The second argument is that no treatment controls would also be exposed to risk of local infection if they had their blood drawn as often as those children who received the drug. This is a good argument. I do not know, but would like to discuss if there are differences in risk between a needle stick for blood draw and an IV placement which stays in place for several hours. If so, then this argument is weakened.

4. Use of a placebo which is unpleasant and stressful. This stress may be immunosuppressive.

There is growing acceptance of the detrimental physical effects of emotional stress. The field of psychoneuroimmunology is examining the relationship between stress and immune function. Both animal and human studies have shown detrimental effects on immune function during or following stress. The stress of an IV may be outweighed by the potential benefits of the drug. Surely it cannot be outweighed by a placebo, even if the child is given excellent care and attention during hospital visits. This factor must be considered when analyzing the emotional and physical benefits of the placebo effect.

5. Endpoints.

A. In our discussion with physicians and others at Children's Hospital in Oakland, we were shocked that they were unable to answer our questions about end-point with other than the response of "2 years." Two years is the length of the trial, not the definition of the endpoints. They have agreed to respond to this concern and tell us if death is the endpoint. If it is, we believe that they will work with us to find much less severe and life-threatening end points.

B. The description of protocol 051 provided by NIAID states, "Patients are followed for the development of **serious bacterial**

ivig2

6/14/89

infections, as well as for a number of factors relating to safety, tolerance, progression of disease and **survival**" (my emphasis). The frightening implications is that endpoints short of death and serious illness are not defined. If this is so, the end points of this trial must be changed.

C. At what point of illness is a patient/subject's status unblinded? Does the patient have the option of receiving the IVIG if s/he had been receiving the placebo? Will the study continue to pay for the drug and medical care in this case?

6. **AZT intolerance.** Since protocol 051 includes AZT, we are concerned about the issue of AZT intolerance. What happens to children who can't tolerate AZT? Are they given the opportunity to receive IVIG without AZT? Is AZT tolerance determined before the study begins. If not, is it followed closely during the study? Is AZT intolerance factored into the data analysis. Are the AZT intolerant discriminated against in a sense in this study if they don't have alternative access to the IVIG that is affordable?

6/13/89

To: Human Research Committee
UCSF

From: Hank Wilson

Member of ACT UP Treatment Issues Committee

Subject: IVIG Protocol 051 and 045

The Treatment Issues Committee of ACT UP wishes to meet with the Human Research Committee to discuss the IVIG Protocol 051 and 045. It is my understanding that committee member Ric Puglia sent a letter protesting the IVIG trial and requesting a meeting with your Human Research Committee. To date, we have had no reply. I have called Dr. Weintraub but my calls were not returned.

We are concerned with several issues:

1. Use of a placebo in children facing a life threatening disease.
2. Use of a placebo when non placebo alternatives exist.
3. Use of an IV placebo with potential for infection in children who may already be immunosuppressed.
4. Use of a placebo which is unpleasant and stressful which may suppress immune function.
5. Endpoints. Are the endpoints specified? Do the endpoints provide for unblinding the status of a particular participant's status if the participant's health declines? Is crossover to getting the drug allowed for placebo recipients if their health declines?
6. AZT intolerance. Is AZT toleration determined? Prior to the start of the trial? Are their endpoints for administration of AZT?

I have attached the Wall Street Journal article on IVIG placebo trials. We share concerns raised in the article. You are aware of the protest ACT UP has called for June 17. A meeting may help to establish the facts and resolve, clarify some of the concerns we have with IVIG placebo trials. ACT UP and our Treatment Issues Committee is diverse in terms of background and training and expertise in medical and AIDS research matters. We are similar in our concern for children with AIDS and HIV.

I may be reached at [REDACTED] and committee member Michelle Roland may be reached at [REDACTED].

Thankyou for your consideration.

Hank Wilson
Hank Wilson

[REDACTED] [REDACTED] [REDACTED] [REDACTED]

DRAFT

Response to Hank Wilson, ACT UP Treatment Issues Committee,
letter dated 6/13/89

Note: These responses should be reviewed with Dr. Diane Wara,
476-1736.

Responses to the issues you raised:

1. The Committee on Human Research (CHR) in their review considered this concern as it would in any clinical research study. As did the investigators, the CHR thought it essential to have a placebo control since the IVIG treatment involves sufficient risk and costs that it is important to clearly establish its efficacy. The clinical endpoints (for example, diminished bacterial infection) are imprecise enough that a control group is essential to minimize the possibility of falsely concluding that IVIG is acceptable treatment and thus in the process needlessly subjecting untold numbers of children to needless risk and discomfort in the future. All participants in the IVIG study will receive AZT, of course.
2. This is partially addressed in response #1. In the Committee's opinion, it would be inappropriate not to include a placebo treatment. This is further addressed below.
3. The investigators and others have had experience in the use of albumin infusions in children, including those who were immunocompromised. Such treatment is well tolerated and does not appear to produce infection. It should be noted that the children in the IVIG study are more accurately described as immunodeficient, not immunosuppressed.
4. Yes, the placebo treatments will be unpleasant and stressful -- more to some, perhaps, than to others, but it is a burden to the young recipients. The CHR considered this in assessing the risks/benefits of including a placebo treatment. To omit a placebo group and falsely conclude that IVIG is an effective treatment would in the future subject countless children to needless, unpleasant, and stressful treatments. The Committee was not aware that albumin will suppress immune function. 
5. Yes, the endpoint is specified: it is number of bacterial infections. It is unfortunately an imprecise, somewhat fuzzy endpoint (as compared to, for example, death) but is the best alternative. Thus, the need for a placebo

comparison group. Yes, there is a provision for unblinding and alternate treatment if any participant's health declines.

6. Experience thus far is that children tolerate AZT much better than adults. AZT side effects will be closely monitored. If serious side effects develop, the AZT treatments will stop for that patient.

Richard E. Puglia

JUN 5 1989

HRE

May 31, 1989

Office on Human Research
Box 0616
San Francisco, CA 94143

Attn: Mr. Reese Jones,
Chairman

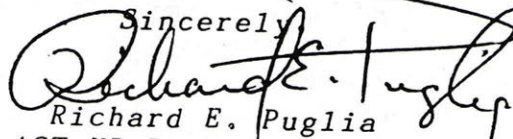
Dear Mr. Reese:

Enclosed is a copy of our proposed demonstration on June 17th against the use of placebos on infants and children with AIDS, i.e. ACTG 051 and ACTG 045.

ACT UP S.F. would like to schedule a meeting with you and the entire Institutional Review Board as soon as possible or preferably no later than June 15th.

We look forward to an expedient response in this matter and to a productive meeting.

Sincerely,


Richard E. Puglia
ACT UP Representative

REP
Encl.

6/13/89

To: Human Research Committee
UCSF

From: Hank Wilson

Member of ACT UP Treatment Issues Committee

Subject: IVIG Protocol 051 and 045

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out computer equipment at California Federal Savings and Loan Association.

Most businesses are ill-prepared to cope with electronic disasters, computer and communications specialists say. That's partly because computers have crept grad-

ices, a unit of SunGard Data Systems Inc., Wayne, Pa. They have nearly 1,500 clients between them, including Chase Manhattan Corp., First Chicago Corp., PepsiCo Inc. and Harlequin Enterprises Inc., the publisher of romance novels.

But the bank's problems lasted only three days. Had they extended through its business period, on Friday and Saturday, "we probably would have had a mutiny on our hands," Mr. Hackert says. "We truly are a creature of the electronic age."

Critics Protest Use of Placebo in Testing Drug Therapy for Kids Who Have AIDS

By MARILYN CHASE

Staff Reporter of THE WALL STREET JOURNAL
The wrenching ethical debate over the use of placebos in testing AIDS therapies has moved into the pediatric ward.

Two years ago, the medical community was racked by protests over placebo trials of the drug azidothymidine, or AZT. Now the National Institutes of Health is drawing fire as it recruits some 400 children with acquired immune deficiency syndrome to help test an experimental intravenous treatment. Each month, at one of 30 or so hospital centers around the country, half of the children will receive a potentially helpful infusion of human antibodies; the others will get albumin, the chemical equivalent of egg white.

"These children (on placebo) will surely die during the course of the experiment," asserts Mathilde Krim, a biologist and founding chairwoman of the American Foundation for AIDS Research, noting that the children's average two-year life expectancy matches the length of the test. "It's like giving up on them." (Researchers strenuously disagree.)

The drug being tested is intravenous gamma globulin, known as IVIG, which is made from pooled human serum containing antibodies to a variety of microbes. The question is whether it can prevent bacterial infections causing sepsis (blood infection), meningitis and pneumonia, which often strike children with AIDS. Though the official number of such children today is 1,000, as many as 3,000 are feared sick, and it's estimated another 20,000 will be infected with the AIDS virus by 1991.

Promising Signs

IVIG is already an approved treatment for a variety of conditions, including other childhood immune deficiencies, and it is available to AIDS patients at a number of clinics. While it won't cure children of AIDS, preliminary studies suggest it could make them more comfortable and perhaps help them to live longer. However, a large-scale, formal test like NIH's is needed to prove its safety and effectiveness, says Anne Willoughby, co-director of the study.

The promising signs were seen several years ago in pilot studies performed by a pair of AIDS specialists—Arye Rubenstein of Albert Einstein College of Medicine in New York, and James Oleske of Children's Hospital of New Jersey, in Newark. Dr. Rubenstein found fewer cases of fever and sepsis in treated children; Dr. Oleske reported some extension of survival.

These studies, though, were small and weren't placebo controlled. Dr. Oleske, who provides IVIG to AIDS patients at his clinic, unsuccessfully tried to get funding

in 1984 for a larger, follow-up study.)

A placebo—the Latin word for "I shall please"—is a medically inactive substance given to the control group in a drug test. In a randomized trial, where neither doctor nor patient knows who is getting what, a placebo helps to ensure objectivity.

But critics of the NIH study, including many AIDS activists, argue against placebos on ethical grounds. They object to giving a dummy drug to anyone with a fatal illness, particularly to children who can't speak for themselves. To protest the use of placebos in the trial, a New York activist group called ACT UP (AIDS Coalition to Unleash Power) hurled questions and distributed leaflets at a pediatric AIDS conference last month in Newark, N.J.

"We shouldn't use placebo unless there is no reason to believe, none at all, that the treatment group will fare better than the untreated group," says AMFAR's Mrs. Krim. The studies by Drs. Rubenstein and Oleske do suggest there will be a difference, she contends. Furthermore, she says,

WHILE the drug isn't a cure, preliminary studies suggest it could make children more comfortable and perhaps help them to live longer.

historical controls—in this case, knowledge of how untreated children have fared in the past—provide sufficient comparison.

Robert Levine, an ethicist at Yale University Medical School, says he's generally opposed to placebos unless a test drug is scarce—which isn't the case with gamma globulin.

Apart from the objections to placebo use in the study, there are concerns about IVIG itself. For one thing, it isn't totally benign, says Anne Petru, who heads the branch of the NIH trial at Children's Hospital of Oakland, Calif. Dr. Petru says she has witnessed three cases of IVIG-induced anaphylaxis, a rare but overwhelming allergylike reaction that can entail respiratory distress and even death.

For squirming toddlers, the three-hour to four-hour infusions are hard to take. Tiny veins are hard to find. The child's arm must be immobilized on a board to keep the needle in place. In Dr. Oleske's IVIG clinic, children sometimes need sedation or restraints.

Supporters of the test, in which about 300 children are enrolled so far, defend it as pursuit of the greatest good for the

greatest number. "It may be that the most ethical thing to do is to come to a rapid answer so that the most patients benefit from the result," says Keith Krasinski, a doctor at Bellevue Hospital in New York.

The use of the placebo is "very controversial, but it has to be done," adds Dr. Petru of Oakland. "If (IVIG) were \$10 a bottle and 100% safe, all kids would be getting it." (IVIG costs about \$400 for each child's monthly dose.)

As for relying on historical controls, researchers respond that this is imprecise and risks meaningless comparisons. For example, if the past untreated patients were sicker than those currently receiving the drug, improvements attributed to the drug might be an illusion. Another worry is that if a doctor knows his patients are getting the drug, unintentional bias could color the doctor's evaluation.

Researchers suggest, too, that the study can bring even placebo recipients the benefit of regular medical attention. And there is a monitoring board watching for any improvement in the IVIG group, which could eliminate the need to continue the trial.

Mixed Emotions

Dr. Oleske himself has watched the trial unfold with mixed emotions. He helped to design the study, but he refused to participate in the tests involving the sickest children because he feels the drug has already been moved effective for them. "We felt comfortable with our experience dating back to 1981," he says. He adds that he isn't able to take part in the other section of the NIH trial, testing IVIG in children who are less sick, because of limited resources and his involvement in a pediatric test of AZT.

The decision to cast a child's fate with a randomized study isn't an easy one for parents to make. Moreover, these parents are often poor, AIDS-infected IV drug users. Even when a child is in foster care, biological parents must be tracked down.

Some parents sign up out of "social-mindedness," says Peggy Weinrub, who heads a branch of the NIH study at the University of California at San Francisco. But "many parents would prefer their kids get the real thing," she adds.

Such was the decision of the Starcross Community of Sonoma County, Calif., a Catholic order that cares for children with AIDS. The order declined Dr. Weinrub's invitation to place one of its children in the trial, opting instead to seek monthly IVIG treatments for the baby girl. "If there was a chance she would benefit, we wanted her to have it," explains Mary Martha Aggeler, a lay sister at Starcross. IVIG, she says, "seems to help them live longer, and that's good enough for me."

Wall Street Journal
5/31/86

Examiner 6/13/89

ACT UP rips AIDS-baby tests

Wants to halt placebo use at Oakland hospital

EXAMINER EAST BAY BUREAU

OAKLAND — An AIDS advocacy group has lodged a complaint with officials at the Children's Hospital here over placebo tests of AIDS drugs on babies.

Members of AIDS Coalition to Unleash Power (ACT UP) met Monday with medical researchers at the hospital in efforts to halt the 16-month-old program, which is under way at Children's, the UC Medical Center in San Francisco and 30 other hospitals throughout the nation.

Tests are being supervised by the National Institutes of Health and are scheduled to run for two years.

Under the program, babies infected with the AIDS-causing virus at birth are tested, upon parental consent, with some infants receiv-

ing experimental drugs and others receiving a placebo to test comparative results.

Michelle Roland, speaking for ACT UP, said Monday that infants receiving the placebo were placed in a more life-threatening situation in the name of research.

"We're saying that we don't know if the experimental drugs will work, but at least the babies have more of a chance than if they receive a placebo," Roland said. "We don't want babies becoming sacrificial lambs."

Ryan Rubio of ACT UP said because of the dangers of the human immunodeficiency virus, "researchers must be more creative than to rely on the traditional placebo testing methods."

Medical officials at Children's Hospital defended testing methods prescribed by the NIH.

David Fielder, vice president in charge of research and clinical programs at the hospital, said procedures were "among the most effective in testing the authenticity of the treatment protocol."

Fielder said great care was taken to "guard against additional infection."

Researchers will review all policies and protocol regarding this testing, he said, and we will continue communicating with coalition members.