

ACT UP

AIDS Coalition To Unleash Power

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ACT UP / NEW YORK RELEASES "TREATMENT AGENDA 1990,"
INCLUDING 99 NEW AIDS DRUGS FOR CLINICAL TRIALS, AND
RECOMMENDATIONS FOR FASTER PHASE I STUDIES.

-- Activists outline Sweeping Changes in AIDS Research --

ACT UP / New York, the AIDS Coalition to Unleash Power, today issued its AIDS Treatment Research Agenda for 1990 at the Sixth International Conference on AIDS in San Francisco.

At last year's AIDS Conference in Montreal, ACT UP's National AIDS Treatment Research Agenda led directly to the Parallel Track program for access to experimental AIDS therapies for people intolerant of standard therapy, or unable to participate in controlled clinical trials. It also led to the expanded access program for ddI, giving 10,000 Americans who could not tolerate AZT, the only approved anti-HIV drug, access to alternative therapy.

This year's Treatment Agenda summarizes ACT UP's demands of the US AIDS research establishment, including:

- 1) A coordinated, comprehensive effort to develop therapies effective against all serious and fatal complications of HIV infection. [Today's research focuses on anti-HIV therapies like AZT and ddI, while ignoring the opportunistic infections that kill over 90% of people with AIDS.]
- 2) A list of 99 new drugs ready for Phase I studies in humans, but are not yet in clinical trials. ACT UP member Bob Huff said "the bottleneck in AIDS treatment today is getting new drugs with promising test-tube activity into people. Our Agenda provides scores of drugs which might extend the lives of people with AIDS by years or decades. If they're not tested, this chance, and their lives, may be lost forever."
- 3) Recommendations to streamline the crucial Phase I studies that first evaluate new drugs in humans. Said ACT UP member Garance Franke-Ruta, "Today's Phase I trials fail to gather crucial information -- like the lowest effective dose of AZT, something which we still don't know. Instead, they gather too much irrelevant data. They can do Phase I trials twice as fast, and gather twice as much useful data."

(more)

"If a drug is proven safe in Phase I, with our recommendations, they will be eligible for Parallel Track. At the same time, carefully conducted Phase II/III studies will fill in the gaps about how best to use them."

- 4) A history of the development of the Parallel Track program -
- forged in an unprecedented alliance between ACT UP and AIDS scientists like Anthony Fauci of the National Institutes of Health (NIH) and Ellen Cooper of the Food and Drug Administration (FDA).

ACT UP builds on the concept of Parallel Track, proposing a "Middle Track," through which key information about a new drug's efficacy could be gathered under Parallel Track.

- 5) Recommendations to speed up all phases of AIDS drug trials, while gathering better data and expanding access to previously underrepresented groups such as women, people of color, drug users, adolescents, children, infants and homeless people with HIV.
- 6) ACT UP demands that the Bush Administration double the entire biomedical research budget -- not just for AIDS. ACT UP demands that the NIH AIDS research program restructure, reprioritize, and open the scientific system to people with AIDS and activists. In addition, ACT UP encourages AIDS activists and people with AIDS to get involved in research, set up community based research institutions, and make their voices heard in existing research programs.

According to Mark Harrington of ACT UP/ New York's Treatment + Data Committee,

"People with AIDS are very pessimistic right now. No new treatments for HIV are emerging from Phase I trials. Good treatments for opportunistic infections exist, but they aren't being studied, and those that are approved aren't available to the people who need them. We are trying to counteract that pessimism with constructive suggestions for change. If the Federal AIDS program tests even half of the 99 drugs we've unearthed, we could turn this epidemic around. Publicly funded research must be accountable to the people it's for. That's the message of our Treatment Agenda for 1990."

ACT UP

A Week of International AIDS Activism

FOR IMMEDIATE RELEASE

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The AIDS Coalition to Unleash Power

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AIDS Action Planning
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Gay/Lesbian March
Activists
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PWA Coalition of
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STAT
The Swamp Rats
Tennessee Gay/Lesbian
Coalition/ACT UP

ACT NOW
The AIDS Coalition to
Network Organize
and Win

Kevin Farrell, ACT UP/Los Angeles
Paul Feldman, ACT UP/Seattle
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PRESS ADVISORY

JUNE 21, 1990

ACT UP/NEW YORK TO RELEASE 1990 TREATMENT AGENDA

-- Activists outline sweeping changes in AIDS research --

The AIDS Coalition To Unleash Power (ACT UP)/New York will be holding a press conference at 12:30pm on Thursday, June 21, at the Diva Hotel, 440 Geary St. (near Union Square) to release its AIDS Treatment Research Agenda for 1990. The document strongly criticizes the AIDS research effort of the United States government, and proposes sweeping revisions to improve the quality and quantity of AIDS treatment research.

"So far, federal AIDS research has been murderously irrelevant to the lives of people with AIDS," said ACT UP/NY member Mark Harrington. "This Research Agenda is our program to ensure that research is producing viable treatments and not just higher trading prices for pharmaceutical company stocks."

The Treatment Research Agenda documents the paucity of new treatment approaches ready for wider, Phase II testing. The paper also contains proposals for speeding up all phases of AIDS research and outlines a new "Middle Track" program, similar to the "Parallel Track" expanded access program, but allowing for more data collection on a drug's efficacy.

ACT UP/NY is a diverse, non-partisan group of individuals, united in anger and committed to direct action to end the AIDS crisis. ACT UP has demonstrated at the White House, the Food and Drug Administration, the Centers for Disease Control, and most recently, the National Institutes of Health. There are now over sixty ACT UP chapters internationally, including West Germany, Australia, France, and Great Britain.

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June 21, 1990
PRESS ADVISORY

ACT UP AND ACT NOW CALL FOR PRESS CONFERENCE TO DISCUSS POLICE VIOLENCE

The AIDS Coalition to Unleash Power (ACT UP) and the AIDS Coalition to Network, Organize and Win (ACT NOW) will hold a press conference today at 2:00 p.m. outside the George Moscone Center, one of the sites of the Sixth International Conference on AIDS and the site of yesterday's opening day direct action marred by police violence.

Yesterday, one protester, while in police custody, requested a cup of water with which to take medication and was given a cup containing poisonous cleaning fluid by a police officer. A doctor and a poison control unit had to be called after the protester drank some of the liquid.

Attending the press conference will be some of the protesters who this week have been injured. At least two demonstrators at Wednesday's activities were treated at local hospitals for injuries received at the hands of San Francisco police. Press will have an opportunity to ask questions of these protesters.

ACT UP and ACT NOW are nonviolent, direct action groups. There have been no reports or allegations of violence by the demonstrators directed toward police or others.

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ACT UP

ROUTING AND TRANSMITTAL SLIP		Date 6/27/90	
TO: (Name, office symbol, room number, building, Agency/Post)		Initials	Date
1. Statistical Working Group			
2.			
3.			
4.			
5.			
Action	File	Note and Return	
Approval	For Clearance	Per Conversation	
As Requested	For Correction	Prepare Reply	
Circulate	X For Your Inform	See Me	
Comment	Investigate	Signature	
Coordination	Justify		
REMARKS			
Attached is a copy of the 1990 edition of the ACT UP AIDS Treatment Research Agenda for discussion at the Statistical Working Group meeting on July 10, from 1-5:30 p.m. I'm looking forward to seeing you at this meeting.			
FROM: (Name, org. symbol, Agency/Post)		Room No. ----Bldg.	
Dr. Susan S. Ellenberg, Chief Biostatistics Research Branch Division of AIDS, NIAID, NIH		214P CDB	
		Phone No. (301) 496-0694	
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ACT UP

Treatment & Data Committee, New York

AIDS Treatment Research Agenda

VI International Conference on AIDS
San Francisco

June 1990

TREATMENT AGENDA 1990

ACT UP / New York

Treatment + Data Committee

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- VI "International" Conference on AIDS -
San Francisco
June 1990

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I. INTRODUCTION: Science in a Crisis

We have lost the war against AIDS. Millions who need not die so young will die so young... Even if a cure were found tomorrow, the system would not test and make it available fast enough to save us.

- Larry Kramer¹

The problem of AIDS is still with us.
We still have not achieved cure.

- Daniel F. Hoth
Director, Division of AIDS
NIAID, NIH²

We are all dying.

- Tofa, a 26-year old man
Uganda³

*

In the tenth year of an epidemic which may be with us all our lives and end some of them, the remaining forces are gathering in one of the cities where it first appeared. Three ghostly entities will face each other at the Moscone Center in San Francisco when the Sixth "International" Conference on AIDS opens Wednesday afternoon: the absence of George Bush, whose silence equals our deaths; the absence of researchers who never went after AIDS because there were no research funds; and the absence of 80,000 Americans (and hundreds of thousands of people around the world) murdered by the ghastly alliance between a tiny piece of fucked up data (HIV) and a huge, indifferent bureaucracy (the US government).

After several years of AZT and precious little else in the developed world, and after 10 years of virtually no treatment in the third world⁴, people affected by AIDS worldwide are waking to the recognition that the countries with the resources to end the epidemic -- chiefly the USA -- have no intention of taking the necessary steps. Next year's AIDS budget is smaller than that for the space station "Freedom"⁵. And yet President Bush claims we are "on a wartime footing at the National Institutes of Health. Slashing red tape. Accelerating research. Boosting the budget."⁶

¹ At the second Michael Hirsch awards, New York, 5.90.

² May 15, 1990

³ Jane Perlez, New York Times, 6.10.90, A14.

⁴ Uganda, where in some cities one in four is seropositive, spends but \$1.00 per capita on health care each year.

⁵ US AIDS research budget: \$1.7 billion. NASA space station budget: \$1.8 billion. William J. Broad, New York Times, 6.10.90, p. A30.

⁶ President Bush's first speech on AIDS, 14 months into his term of office.

It's time for a Manhattan Project against AIDS, with a mandate from the highest levels of the US government and endowed with whatever resources it takes to get the job done.

The likelihood of this happening is virtually nil.

Among the communities affected by the disease, prolonged exposure to its realities is provoking not denial but despair and desperation. This year, the hopes of many in the AIDS communities have reached a low ebb. It is clear to all that anti-HIV agents such as AZT, ddC and ddI will not, in any conceivable combination, stop the progression of HIV infection -- at most, for those who are lucky, they will significantly slow it.

At the same time, no new anti-HIV agents have emerged from phase I studies ready for wide-scale trials. This is largely because there have been few phase I studies of new anti-HIV drugs over the past year. New drugs by the dozen are emerging from laboratories around the world, but those in charge of the US AIDS research effort have chosen to focus on conducting wide-scale post-marketing studies of existing treatments (chiefly AZT), while virtually ignoring most of these new approaches.

This must change. Without a commitment to developing new anti-HIV agents from the test tube through phase I/II studies, as well as significantly expanding the scope of opportunistic infection prophylaxis and treatment, and cancer treatment, the US AIDS establishment is abandoning hundreds of thousands of people with HIV to a world of impoverished therapeutic alternatives.

Even those therapies which have become available over the past year -- e.g., aerosolized pentamidine, DHPG, fluconazole, and (for some) ddI and EPO -- are unavailable to most of the people who need them. The government has done nothing to implement last year's PHS recommendations on monitoring HIV infected people to provide early antiretroviral intervention and prophylaxis against PCP when needed. Hence, pneumocystis is still the most common AIDS-defining event.

In spite of the overwhelmingly bleak reality which surrounds us as the AIDS epidemic enters its second decade, there are some new alliances which are worth noting:

- * Activists worked with NIH researchers and the FDA to design the "Parallel Track" program for systematizing expanded access to certain new therapies, and then with Bristol Meyers to design the ddI expanded access protocols; such coordination and cooperation must become the rule, rather than the exception.
- * Activists are working with community-based clinicians, NIH biostatisticians and researchers on the design of the Multiple Opportunistic infection Prophylaxis (MOPS) study for the Community-Based Clinical Trials Network (CBCTN) and the SOCA (Study of the Ocular Complications AIDS) trial of DHPG vs Foscarnet in CMV retinitis. NIH biostatisticians established the Statistical Working Group (SWG) within the ACTG to provide a forum where activists, researchers and statisticians can work together to streamline old studies and create innovative new models for clinical research.
- * After ACT UP struggled with NIAID Division of AIDS officials to attend ACTG meetings, the NIAID established a Patient Constituency Working Group (PCWG) to represent people with HIV and affected communities within the ACTG; subsequently, the ACTG Executive Committee recommended that each ACTU establish a community advisory panel. This should be the model for all AIDS trial sites, community-based and academic.

The following three objectives will define the core arena for AIDS treatment activism in the coming year:

- * **Broadened research priorities**
- * **Innovative clinical trial designs**
- * **Vastly expanded health care and treatment access**

One year ago in Montreal, ACT UP proposed its National AIDS Treatment Research Agenda. The most tangible result was the expanded access program for ddI, which enabled 10,000 Americans to receive this potential therapy in a prototype for Parallel Track. At the same time, however, and more deeply felt in the communities affected by AIDS, was the loss of tens of thousands of people, and new diagnoses for tens of thousands more.

AIDS is causing an abrupt and seismic shift in biomedical research. The outlines of a new research order are emerging. Some scientists are changing, adapting to this new order. History will record the names of those who assist in creating a more equitable, humane and efficient research system, and it will record the names of those who resist. It is time to make one thing clear: people with AIDS will win this battle. Science will serve their needs. Either scientists will work with us in advocating change, or they will be forced to step aside. It is time for activists from around the world to make research accountable to the needs of people, not profit.

There is only so much horror a people can tolerate. Again, this year, we propose the elements of a rational, comprehensive and coordinated research effort to systematically target all the serious and fatal complications of HIV disease. If our message is not heeded within the coming year, the rapidly diminishing hopes of our communities will vanish. What will happen then?

*

II. DISEASES + DRUGS TO STUDY

A. Research Priorities Revisited

* HIV and the Human Immune System

Virology as a clinical science is still embryonic. The first 10 years of HIV research have been based on models derived from DNA viruses like herpes simplex. Thus, Burroughs-Wellcome, developer of the HSV DNA chain terminator Acyclovir, applied this technique against HIV with AZT. Eventually it became clear that dideoxynucleoside analogues have only limited efficacy in HIV disease. New pathogenetic explorations and clinical approaches are needed. They are not being explored.

During the era of AIDS, great strides have been made in virology and immunology. Yet even those investigators who have found intriguing laboratory results have not yet applied these insights to treatment research.

For example, work carried out in the Laboratory of Immunoregulation at the NIAID has shown that herpesviruses, including HSV, CMV and EBV, accelerate HIV production by stimulating tumor necrosis factor (TNF), which, in turn, stimulates HIV. This "positive feedback loop" may contribute to the wasting (cachexia) and anemia associated with AIDS.

The obvious clinical corollary would be initiation of anti-HSV therapy as soon as HIV infection was diagnosed. Long before HSV or CMV infections become clinical, they may be assisting HIV in its

subversive assault on the immune system. Yet no studies have been undertaken of acyclovir, for example, in asymptomatic HIV infection. Many people with HIV are taking the drug on their own.

For several years, prevailing dogma held that HIV, and HIV alone, led to AIDS. Now, many of the once most ardent defenders of the "HIV is necessary and sufficient" dogma have reversed their views, and a wild hunt is on for the various co-factors -- other pathogens and native human proteins -- which may accelerate HIV-associated immunosuppression and its complications.

Theories of Viral and Cytokine Co-Factors for AIDS

<u>Proponent</u>	<u>Viral Cofactor</u>	<u>Cytokine Cofactor</u>	<u>Postulated Effect</u>	<u>Year Proposed</u>
Sonnabend		IFN-alpha	AIDS	1982
Sonnabend	CMV, HSV		AIDS	1983
Fauci	CMV, HSV		Synergistic w/ HIV	1988
Fauci		TNF-alpha	AIDS; cachexia, anemia	1989
Gallo	HTLV-I		AIDS	1982
Gallo	HTLV-IIIb		AIDS	1984
Gallo	HHV-6		Synergistic w/ HIV (?)	1989
Gallo		FGF, PDGF	KS	1990
Miles		IL6, TGF-beta	KS	1990

Viral cofactors: CMV = cytomegalovirus; HSV = herpes simplex virus (1+2); HTLV = human T cell leukemia (or, once, lymphotropic) virus; HHV = human herpes virus. Cytokine cofactors: IFN = interferon; TNF = tumor necrosis factor; FGF = fibroblast growth factor; PDGF = platelet-derived growth factor; IL6 = interleukin-6; TGF = transforming growth factor.

Joseph Sonnabend first noted the unusual presence of circulating alpha interferon in the blood of people with AIDS in 1982. This insight was ignored in the mad rush to "zap the virus" once it was discovered, and in the late 1980s when cofactors became the rage, Sonnabend's contributions were not acknowledged.

Some investigators have proposed attempting to control obvious abnormalities associated with AIDS, even in the absence of a complete understanding of their etiology, as a therapeutic strategy. Others propose using the very cytokines found in abnormal quantities. This leads to the paradoxical situation we are in, where some advocate using anti-interferon antibodies, and others prescribe recombinant alpha interferon as treatment. Similarly, Genentech is testing recombinant tumor necrosis factor while NIH investigators are proposing anti-TNF antibodies. Perhaps head-to-head comparisons of "therapeutic" cytokines against their "therapeutic" antibodies might resolve this dilemma.

It is quite possible that some of these abnormal growth factors may represent the body's attempt to fight off the effects of HIV. Circulating interferon, for example, might be a vain attempt to mobilize the body's antiviral defenses. Perhaps this accounts for the purported anti-HIV effects of interferon when administered earlier in infection.

Similarly, some of the growth factors recently proposed as elements in the pathogenesis of Kaposi's sarcoma -- e.g., FGF, TGF-beta, IL-6 -- might be produced to inhibit HIV, but have the untoward effect of accelerating the virulence of KS. Hence, antagonizing them with treatments might vanquish the KS, but accelerate the HIV disease process. Recently, it has been proposed that herpes viruses gain entry into cells by 'hitching a ride' on fibroblast growth factor (FGF).⁷ Perhaps, if this is so, this provides yet another mechanism for HSV-associated TNF and KS-associated FGF to accelerate HIV disease.

⁷ DP Hajjar, Science, 6.15.90.

In the absence of a convincing global explanation for HIV's pathogenicity, it is imperative that diverse hypotheses be examined, both in the laboratory and in humans. It is evident that the dogmas of single agent therapy are outdated.

New approaches should be based on how the actual disease (as currently manifested) presents itself clinically, rather than on perspectives derived from the primitive antiviral work which preceded it. We still cannot cure any viral disease. Approved agents (Acyclovir, AZT) are only virustatic, not virucidal. Thus, retroviral theoreticians must descend from their ivory towers to intervene on each of the clinical complications of AIDS to make real progress.

* Opportunistic Infections and Cancers

All too often, the opportunistic complications of HIV infection have been regarded as mere "noise" distracting from the underlying HIV "signal." People with AIDS have been forbidden OI medications or thrown off anti-HIV drug trials when they developed such complications. This metaphysical preference for using mediocre anti-HIV drugs and forbidding effective anti-OI prophylaxis and treatment led to much unnecessary sickness and death.

ACT UP's call to make the major AIDS-associated opportunistic infections preventable by 1991 seems to have fallen on deaf ears. The last year has seen an increase in plans to conduct prophylaxis trials, but few have gotten off the ground.

Pneumocystis carinii. PCP remains the leading OI at AIDS diagnosis⁸, in spite of the development of effective prophylaxis. The US government remains unwilling to subsidize the nationwide screening and prophylaxis necessary to make PCP a thing of the past. This is genocide by indifference. If this pattern continues, at least 260,000 new cases of PCP may occur by the end of 1993.⁹ A day in the hospital with PCP costs more than a year of aerosolized pentamidine prophylaxis; Bactrim and Dapsone are even cheaper than this overpriced LypoMed orphan drug.

Other troubling research questions are coming to the fore: 1) PCP breakthrough in spite of prophylaxis (which seems to be on the increase, especially for people on aerosolized pentamidine), 2) diagnosis and treatment of extrapulmonary pneumocystosis in people on aerosolized pentamidine, 3) adoption of guidelines for prophylaxis in children with HIV, 4) how to revive the ACTG's stalled studies of trimetrexate for treatment of refractory PCP, 5) what is the best dose and nebulizer for optimizing use of aerosolized pentamidine, and 6) is daily systemic PCP prophylaxis with Bactrim or Dapsone better or worse than intermittent dosing. DFMO (eflornithine) is another promising agent lost in development. Burroughs-Wellcome has a new compound, 566C80, which kills the pneumocystis organism and is non-toxic, at least in early human trials.

One ACTG study, 081, compares three anti-pneumocystis agents to see which provides the best protection against PCP, and whether local (aerosolized pentamidine) or systemic (Bactrim or Dapsone) prophylaxis is most useful. It enrolled its target 450 subjects in record time, and recently expanded accrual to 600. A nested study of Fluconazole vs Clotrimazole for fungal prophylaxis (ACTG 981) enrolled equally fast. This shows that the ACTG can enroll subjects quickly in a well-designed, clinically relevant OI prophylaxis trial. Its task now should be to expand prophylaxis studies to CMV, MAI and toxoplasmosis.

⁸ Lawrence K. Altman, New York Times, 6.12.90.

⁹ PHS estimate of total AIDS caseload by end of 1993: 400,000 -- including 260,000 new cases. Without prophylaxis, PCP occurs at AIDS diagnosis in 60% of cases and eventually in 80%.

Cytomegalovirus (CMV) treatments remain highly toxic and invasive. Between 10-25% of PWAs develop disseminated CMV infections (26,000-65,000 cases by 1993). Evidence from Fauci's lab and others indicates even subclinical CMV can accelerate the progression of HIV disease. Five steps, then, are essential: 1) immediate FDA approval of **Foscarnet**; 2) study of anti-CMV medication as a form of "cofactor control" in asymptomatic populations; 3) study of oral anti-CMV agents for prophylaxis of disseminated disease; 4) development of oral anti-CMV agents for treatment, to obviate the need for dangerous catheters; and 5) FDA approval of **DHPG** for CMV colitis and other disseminated forms of CMV disease. Drugs to watch out for: **HPMPC**, **PMEA**.

Toxoplasmosis. Some researchers estimate 30% of the HIV infected population overall is positive for antibodies to *Toxoplasma gondii*. Of those infected, about 1/3 go on to develop toxoplasmic encephalitis. If 10% of all people with AIDS are at risk for toxoplasmosis, there may be 32,000 cases by the end of 1993. The ACTG has opened one trial for treatment of toxoplasmosis (pyrimethamine/sulfadiazine vs pyrimethamine/ clindamycin); it has enrolled at a snail's pace (1 person every 2 months) for a total of 3 subjects.¹⁰ Community-based clinical trial sites have been discussing several toxoplasmosis prophylaxis protocols for over a year now; they should stop talking and start the studies.

Mycobacterium avium complex (MAC, a.k.a. MAI) affects between 50-75% of people with advanced AIDS¹¹ (> 130,000 cases by 1993). The ACTG has yet to open a single trial for treatment of this chronic wasting disease, although one is on the drawing board. Pharmaceutical sponsor **Adria** despaired of the ACTG and is conducting its trial of **rifabutin** (ansamycin) for MAC prophylaxis through community based research groups. New macrolides such as **clarithromycin** and **azithromycin** offer the promise of better anti-MAC activity without the toxicity of today's multi-drug regimen.

Fungal Infections, including candida, cryptococcosis, histoplasmosis and others will become more readily treatable with the recent FDA approval of **Fluconazole**. The downside is this **Pfizer** drug's price; at \$4,000 per year for cryptococcal maintenance, this drug costs more than AZT at the new lower price and dose. Yet, because it is oral, Fluconazole offers the hope of providing effective prophylaxis against serious fungal infections, and remission of chronic candidiasis. **Janssen's** rival triazole product, **Itraconazole**, is a cheaper, but still experimental, oral antifungal, and **Schering's** new **SCH 39304** seems to be coming along fast; it's oral and non-toxic.

Other opportunistic Infections, while rarer than the five major pathogens, demand intensified research. These include several already designated under the rubric of AIDS by the CDC such as **progressive multifocal leukoencephalopathy**, which has responded to crude antivirals such as **Ara-C** -- newer antivirals should be tested against PML; and **cryptosporidiosis**, which remains a devastating affliction for 5-10% of PWAs. While early results with **Diclazuril** and IV **Spiramycin** suggest potential benefits, the best dosage of the former may be higher than those yet tested, and the latter is, unfortunately, intravenously administered. There are several newly discovered pathogens whose contribution to HIV disease is still unclear, such as **microsporidia** and **mycoplasma Incognitus**. The former responds to no known treatments, while the latter (if Lo's work is confirmed, and its pathogenicity documented) seems responsive to **doxycycline** and several other antibiotics.

HIV associated neoplasms are being treated with highly toxic therapies used for other cancers. Most of these cancer drugs are unpleasant and immunosuppressive; sometimes they are fatal. There are persistent suggestions that **Kaposi's sarcoma** and **non-Hodgkins lymphoma** may be linked to

¹⁰ ACTG 077P, accrual = 3, NIAID Clinical Trials at a Glance, 1.12.90.

¹¹ According to S. Nightingale at the FDA Anti-Viral Drugs Advisory Committee, 4.90.

unknown or unproven pathogens -- KS to some undiscovered organism, the lymphomas to Epstein-Barr virus, while Papilloma virus related anogenital, especially cervical cancer, appears to also be a growing problem. If these suspicions could be confirmed, and agents found, perhaps cancer prophylaxis could be implemented.

Several competing teams are working on the pathogenesis of KS. While it seems to be accelerated by HIV-associated growth factors (the tat gene may upregulate interleukin-6 -- IL-6 -- and transforming growth factor beta -- TGF-beta), there may be an underlying organism responsible. HIV's ex-discoverer Robert Gallo claims to have a non-toxic agent which knocks out KS in vitro, but isn't telling anyone what it is, leading to suspicions that patent concerns are delaying the development of a major breakthrough against KS. Gallo's agent should be exposed and subjected immediately to clinical trials.

**"You cannot rule out the possibility that there
is a carcinogenic effect from the AIDS drugs."**

- Samuel Broder¹²

Recently detected increases in the rate of lymphomas,¹³ in both new AIDS cases and in long-term survivors, raise the troubling issue of whether AZT (which is known to be mutagenic in vitro, and carcinogenic in vivo to female test animals) increases the risk of lymphoma, or whether they are simply a manifestation of later-stage AIDS that AZT assists in helping people survive until. Multi-drug cancer regimens (such as CVP, CHOP, COMP, BACOP, mBACOD, COMLAX and PRO-MACE/MOPP) remain highly unpleasant.

Progress in treating HIV associated cancers has been impeded by the lack of support from the ACTG Executive Committee. The ACTG Oncology Committee is composed of some of the preeminent researchers in the field, and has the highest enrollment of its trials of any ACTG research committee. Nonetheless, in March 1990 the EC cancelled all the Oncology Committee's high priority studies, and assigned it a study the committee did not want (oral VP-16 for KS). The Oncology Committee threatened to resign en masse, and after a showdown with the EC, some of its studies were restored. This story demonstrates that, even within the scientific world, it pays to act up.

B. Pre-Clinical Considerations

Pre-clinical stages of AIDS drug development deserve more intensive scrutiny and decisive changes.

Several powerful test tube compounds have been delayed for years while sponsors scrambled to secure patents and worldwide licensing arrangements. The 2-year delay in starting the clinical trial of trichosanthin (compound Q) is just one example. From all indications, Robert Gallo is holding back from announcing an agent which might treat KS until the Japanese sponsor secures a US patent. These murderous practices, rooted in greed, must cease.

- * **The US Patent Office must expedite review of all potential AIDS treatments.**
- * **Researchers who delay publication or clinical trials while waiting for patent and licensing arrangements should be subject to sanctions, including removal of NIH grants.**

¹² Lawrence K. Altman, New York Times 6.12.90

¹³ Marilyn Chase, Wall Street Journal, 6.11.90; Lawrence K. Altman, New York Times, 6.12.90.

Potential anti-HIV agents are usually screened in immortalized (cancer-derived) T cell lines. These models may be of limited utility; HIV infects over 12 human cell types, and activity in the macrophages may be just as important as anti HIV activity in T cells. Furthermore, for years in the US, anti HIV drugs were screened against the HTLV-IIIB strain of HIV (the one that turned up in Gallo's Petri dish some months after the French shipped him a genetically identical LAV isolate). As one Harvard researcher recently remarked, "we don't see this strain much in the US." Hence:

- * **Lab screens for anti HIV activity should use a variety of cell lines, including T lymphocytes and monocyte/macrophage lineages, and including chronically infected as well as acutely infected cells.**
- * **Lab screens for anti HIV activity should use a variety of HIV strains, including fresh clinical isolates.**

Many months and years are wasted while drug companies replicate work already done abroad in the USA, to meet FDA requirements. With the rapid approach of European economic union in 1992 comes an opportunity for FDA to standardize procedures for acceptance of data developed in Europe.

- * **FDA must set up a process to accept pre-clinical (and clinical) data from abroad.**

Many unnecessary animal studies are done with anti HIV drugs before they enter humans. There is no good animal model for AIDS. Other mammalian lentiviruses each exhibit unique activity, and drugs may work against them, but not against HIV, and vice versa. Mutant species like the rabbit model, the SCID mouse and others may be infectable with HIV, but they do not develop AIDS. (Mice live less than 3 years, much shorter than the latency for HIV, so it is hard to tell what is the relevance of these recombinant rodents).

- * **Pre-clinical animal studies of anti HIV drugs should be restricted to searching for gross organ toxicity, and patterns of pharmacokinetics. Animal studies for carcinogenicity and teratogenicity can be conducted concurrently with phase I trials in humans.**

Many compounds show test tube anti HIV activity because researchers fail to attempt to replicate the situation inside the body. Recombinant CD4, for example, blocks virus binding to T cells in a test tube culture, but when antibodies from HIV positive persons are added, the drug is inert. This may explain CD4's lack of clinical activity.

- * **Test tube assays for HIV binding inhibitors and other agents that work on the viral or cell membranes should compare antiviral activity in the absence and presence of HIV antisera.**

With opportunistic infections, in most cases, there are good animal models for the disease (mouse CMV, cat toxoplasmosis, beige mouse MAC, etc.) In these cases, valuable suggestions of efficacy and dose response can be obtained in pre-clinical studies.

- * **When there is a good animal model for an AIDS associated pathogen, pre-clinical studies should measure the relationship between dosing levels, plasma levels and efficacy.**

The National Cancer Institute (NCI) has a massive program to screen off-the-shelf compounds in vitro for anti HIV activity. Existing compounds should be screened rationally against the various opportunistic pathogens as well.

* NIAID's Development Therapeutics Branch (DTB) should conduct a massive screening program of off-the-shelf compounds for signs of activity against all AIDS associated pathogens, in conjunction with its National Cooperative Drug Discovery Group for Opportunistic Infections (NCDDG-OI).

C. New Drugs for the 1990s

Last year, in Montreal, ACT UP called for the immediate release of ddI, EPO, Fluconazole, Foscarnet and GM-CSF. Since then, over 10,000 people have received ddI through phase II trials and expanded access. EPO has been distributed to over 1,000 people under a treatment IND, and is said to be nearing NDA approval for its AIDS indications. Fluconazole was approved in January 1990. Foscarnet remains unavailable for most people who need it, and manufacturer Astra's promises to sponsor an expanded access program ring even more hollow than they did one year ago. While GM-CSF sponsor Schering-Plough has an ad hoc single patient exemption, GM-CSF also remains far too inaccessible to most people who need it.

There has been virtually no progress in developing seven treatments ACT UP listed as deserving faster testing -- ansamycin, CD4-exotoxin, CD4-immunoadhesin (CD4-IgG), Diclazuril, Hypericin, passive immunotherapy and peptide T. Ansamycin (rifabutin) has entered a multi-center study for prophylaxis of MAC in community-based research sites. The CD4s look less promising this year than last; NIAID nonetheless is proceeding ahead with four ambitious trials. Diclazuril has shown early signs of efficacy at high doses. Hypericin will be lucky to enter a phase I trial (in its synthetic IV form) in July. Passive immunotherapy remains mired in an unattractive dispute between biotechnology companies. Peptide T has completed a trial in Boston, and after much pressure from activists, NIAID and NIMH¹⁴, have agreed to collaborate on a phase II trial.

As activists make increasing headway with regulators, the bottleneck in AIDS drug development seems to recede towards the beginning of the process, when compounds are taken from test tube and animal studies and administered to humans for the first time.

Nonetheless, there are some therapies about which enough is known to licence them immediately on Parallel Track, or approve them. Below are some such treatments, along with recommendations for those in earlier stages of testing, which show enough promise that they should be fast-tracked.

1990: Drugs we need Now

Drug	Indication	Sponsor	Status
Azithromycin	MAC (?), toxo	Pfizer	NDA filed (non AIDS)
ddC	HIV infection	Hoffman-LaRoche	Phase II/III; limited "expanded" access
Foscarnet	CMV, ACV resistant HSV	Astra	Phase II/III
G-CSF	Neutropenia	AmGen	NDA filed
GM-CSF	Neutropenia	Schering/Sandoz	NDA filed
Itraconazole	Fungal infections	Janssen	Phase II
Trimetrexate	PCP, toxo (?)	Warner-Lambert	Phase II/III (endless ACTG); Tx IND

¹⁴ The National Institute of Mental Health -- part of the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA), not part of the NIH. NIAID has not collaborated well, thus far, with its sister institutes.

Treatments for fast-track testing - consider for Parallel Track

Clarithromycin	MAC (?), toxo (?)	Abbott	Phase I/II; approved in France
FIAC	CMV	Oclassen	Phase I (ACTG)
566C80	PCP, toxo, crypto	Burroughs	Phase I (B/W)
Oral DHPG	CMV	Syntex	Phase I (ACTG)
PATH	HIV infection	HemaCare vs Medicorp	Phase I/II
Peptide T	HIV, GI disorders	Integra	Phase I/II
Rifabutin	MAC	Adria	Phase II/III
SCH 39304	Fungal infections	Schering	Phase I (ACTG)
TIBO R82150	HIV-1	Janssen	Phase I (UK)

Treatments for fast-track testing - still Pre-Clinical

BV-ara-U	HSV, VZV, EBV	Bristol-Myers	ACTG "high priority"
HPMPC	HSV, CMV	Bristol-Myers	—?—
Hypericin	HIV, HSV, CMV (?)	ViMRx	ACTG Phase I "imminent"
PMEA	HSV, CMV	Ciba-Geigy	—?—
Protease inhibitors	HIV	Abbott, Merck, Roche, SKB, Upjohn	—?—

The bottleneck in AIDS treatment lies in the failure of Federally funded research programs to bring promising test tube compounds rapidly into Phase I clinical trials.

NIAID officials have told ACT UP that, while conducting more phase I studies was desirable, the ACTG might not be the proper program for carrying out this mission.¹⁵ Yet the intent of Congress, in funding the original AIDS Treatment Evaluation Unit (ATEU) program, predecessor to the ACTG, was to fund small phase I and early phase II trials. As soon as AZT came along, NIAID and its funded investigators eagerly jettisoned plans to test new drugs and took on the task of mapping out AZT's spectrum of activity.

We suggest a reversal of the ACTG's pattern, with the Federal program funding small phase I/II studies, and pharmaceutical sponsors carrying out larger efficacy trials at community based research sites around the country.

ACT UP, at its NIH demonstration on May 21, demanded that NIAID commit itself to test at least 30 new drugs a year in small phase I/II safety/activity studies. In its reply, NIAID called this proposal "arbitrary."

Below are 99 compounds which have been shown to have at least in vitro activity.

Surely at least 30 of these are worthy of NIAID's attention. In July, ACT UP will issue a more detailed report on the diverse classes of compounds emerging from in vitro work, and will work with other groups to develop a consensus about which agents must enter phase I trials this year.¹⁶

¹⁵ June 12, 1990.

¹⁶ This idea comes from John James, of AIDS Treatment News.

99 Compounds that could enter Clinical Trials in 1990-91

* denotes class of agents; - denotes specific compound

60 ANTIRETROVIRALS

- Adenallene
- Aerosolized glutathione
- 2-amino-6-fluorodideoxypurine (FiddP)
- Anti gp 120 antibodies/ high affinity binding primary neutralizing domain (PND)
- Anti interferon alpha (anti-IFN-alpha) antibodies
- * Anti-inflammatory agents
- * Antisense oligonucleotides
- Anti-tumor necrosis factor (anti-TNF) antibodies
- Arachidonic acid inhibitors
- * Aromatic polycyclic diones, including Hypericin, pseudohypericin and soybean saporins
- Aurintricarboxylic acid (ATA)
- BIRG 6587
- Carbovir
- CD4-based peptide derivatives (e.g., CD4 74-92, 81-92)
- CD4-Antibody-pokeweed mitogen conjugate (CD4-Ab-PWM)
- Cyclobut-G
- Cytallene
- * Dideoxynucleoside analogues such as d4C and FddT (FLT)
- FddClUrd (3'-fluoro-2',3'-dideoxy-5-chlorouridine)
- Glycyrrhizin
- HEPT [1-(2-hydroxyethoxymethyl)-6-phenylthiothymine]
- Hydroxychloroquine (plaquenil)
- * Integrase inhibitors
- Interleukin-4 (IL-4)
- Iso-ddA
- Mutant rev
- Mutant tat
- NAC (n-acetylcysteine)
- Oxathiin Carboxaniide (anti-HIV-1 only)
- Oxamyristic acid
- Oxophenarsine
- PATH / passive immunotherapy
- PMEA (phosphopnylmethoxyethyladenine)
- PMEDAP
- * Protease inhibitors (e.g., Roche compound XVII)
- * Ribosome inactivators (e.g., trichosanthin, mormorcharin)
- * Ribozymes
- * RRE oligonucleoside analogues
- * Novel, non-nucleoside RT inhibitors (e.g., Upjohn compounds U-80493, U-78036 + U-76081)
- Soybean saporins
- * Sulfated polysaccharides (e.g., pentosan, carageenan, fucoidan, mannan, lentinan, heparin derivatives, GE-3-S, PVAS, PAVAS)
- * Suramin analogues
- Tamoxifen
- Tat inhibitors (e.g., Hoffman-LaRoche compound TI-1000)
- THA (Tetrahydroacridine)
- * TIBO derivatives such as Janssen's R82150

9 IMMUNE BASED THERAPIES

- * Diethyldithiocarbamate (DTC) analogues
- HIVIG
- IL2/PEG
- Iscador
- Met-enkephalin
- Plasmapheresis
- Post infection vaccines
- Prosorba column
- rgp 160

20 ANTI-INFECTIVES

8 Anti-Protozoals and Anti-Mycobacterials

- * DIMP and other pentamidine metabolites
- Diclazuril
- 566C80
- * Macrolide antibiotics such as Azithromycin, Clarithromycin and Roxithromycin
- TLC-G-65 (Liposomal Gentamicin)

3 Antifungals

- Cilofungin
- Itraconazole
- SCH 39304

9 Anti-Herpesvirals

- BVaraU (bromovinyl-1-beta-d-arabinofuranosyluracil)
- BVDU (bromovinyldeoxyuridine)
- CMV Ig (IV)
- Cyclobut A
- Desciclovir
- HOE 602
- HPMMA and HPMPG
- MSL 109

3 TREATMENTS FOR GASTROINTESTINAL DISORDERS

- Asacol (5-aminosalicylic acid, Mesalamine)
- Peptide T
- Sandostatin

6 CANCER TREATMENTS

- Cimetidine
- Gallo's Secret Japanese anti-KS agents
- Anti interleukin-6 (anti-IL6)
- PF4 (platelet factor 4)
- Sulfonylurea
- 2-cdA (2-chlorodeoxyadenosine)

3 TREATMENTS FOR NEUROPATHY

- Colchicine
- Mexiletine
- Nimodipine

III. CHANGING THE RULES: A Challenge to Clinical Trials Methodology

We have not devoted much attention
to how we actually do these trials.

- Daniel F. Hoth, Director
Division of AIDS, NIAID¹⁷

Because there are many questions to be asked about a drug in the course of its development, and because there are many potential HIV drugs, researchers must be prepared to rigorously set priorities. Arcane studies like the interactions of AZT with probenecid or quinine cannot be justified when there is a crying need for new antiretrovirals to replace AZT. Massive Phase III trials of stop-gap first generation nucleoside analogues can no longer be justified when resources could be better used to capture data from expanded access programs and to conduct smaller, cheaper, faster phase I/II trials of new agents.

Two years ago the bottleneck in bringing new drugs to people who needed them was in the regulatory system; last year, the drugs we needed were held up in phase II/III efficacy trials. This year a large number of new drugs are undergoing pre-clinical development, and many more are stalled, awaiting human testing.

A. RECONCEIVING PHASE I TRIALS

Since Fall 1988, the FDA has provided a mechanism whereby drugs for serious conditions such as AIDS can be approved after two phases of clinical trials. Trial designers must become more creative in order to realize this potential. Phase I trials must now tell us more than they did before. The challenge is to answer the questions about safety normally asked during phase I, while capturing data that will elucidate efficacy and provide insights into practical clinical applications. Here are some suggestions:

* **Phase I trials can produce better information about useful doses.**

In order to answer all the questions that Phase I trials for new anti-HIV drugs now need to ask, they should be staged as phase IA and IB. Phase IA should identify a range of safe, active dosages which fall between the minimum active dose and the maximum tolerated dose (MTD). The maximum tolerated dose can be easily estimated by the method of Collins and Peck (NCI/FDA) who extrapolate the MTD from the dose lethal to 10% of two species of test animals. The minimum active dose can be approximated from in vitro data (and animal data if applicable) combined with early pharmacokinetics studies.

The initiation of efficacy trials should not be postponed by ritual escalation to MTD unless there is a clear suggestion that this information will be useful.

In addition, when determining dosage, phase I studies must consider the concentration of the active species at the putative site of action. For example, in the case of nucleoside analogues, the intracellular half-life of the active triphosphate metabolite, not the commonly measured plasma half-life, is the true parameter of interest.

¹⁷ FDA/NIAID Conference on AIDS Clinical Trials: A Symposium on Methodological Issues, 11.20.90, p. 1.

* **Phase I trials can produce more information about efficacy.**

Once a safe, active dosage range has been established in phase IA, phase IB studies should randomize subjects between dosages within this range. Since these trials are expected to yield efficacy data, subjects should be randomized at the earliest possible point that safety permits. In some studies, such as the NCI's first phase I trial of ddI, subjects with lower T-cells were over-represented in the groups that received lower doses. The poor outcomes of these people were probably due to having few T-cells rather than to the dose of ddI. Yet an unwarranted conclusion was made that higher doses were more effective. This may have contributed to increased incidence and degree of dose-related toxicity during subsequent testing and expanded access. Randomization could have prevented this erroneous conclusion.

It may be that the first, best chance to produce statistically significant efficacy data will come during phase I trials. This chance should not be lost.

* **Phase I studies need to concentrate on determining the lowest effective dosage.**

Currently many phase I trials merely ask "what dosages do not kill?" The lowest effective dosages for AZT, ddC and ddI are still unknown, and the toxicities of currently accepted dosages preclude long-term therapy for most people. In the case of ddC, the drug was almost abandoned after its early, disappointing studies because sponsors did not immediately test the drug at lower, safer doses.

When one considers that people with HIV usually require many medications, it is particularly important to assure that people are not put needlessly at risk by drug interactions due to unnecessarily high doses.

* **Phase I trials shouldn't disregard information relevant to managing toxicities.**

Traditional phase I trials have concentrated on determining which side effects occur and at which doses. A well-designed phase I trial may also capture information about solutions clinically relevant to the management of these toxicities. People with HIV do not always have the luxury of being able to discontinue their medication and switching to another drug.

* **Phase I trials can test combination therapies.**

Since no existing antiretroviral will halt the progression of disease indefinitely, combination anti-HIV therapy needs to be tested. Thus, it is crucial that we learn how to study combinations of drugs during phase I. It may not always be ethically or clinically feasible to study individual new drugs exhaustively before using them in combinations. For reasons of safety, it is better that adverse interactions between study drugs are found early during closely monitored trials rather than during larger post-marketing studies.

Commercial considerations routinely delay or prevent research into optimal combination regimens. Hoffman-LaRoche, for example, is developing ddC as though it would be monotherapy for HIV. Considering its impressively toxic track record, ddC should be considered mainly for alternating treatment.

After basic pharmacokinetics and safety studies new agents developed to treat Mycobacterium avium infection should be tested in combination with the drugs found to be synergistic during in vitro and animal studies -- whether or not the same pharmaceutical sponsor markets them.

* **Phase I trials can test for interaction with concomitant medications.**

Within Phase I trials of anti-retrovirals, researchers should conduct nested studies to determine possible interaction between the study drug and those anti-infective and prophylactic drugs that are in common usage. Phase I trials for anti-infectives will have to test for interaction between the study drug, other anti-infectives and commonly used anti-retrovirals. Therefore, concomitant medication, whether for conditions acute or chronic, must no longer be cause for exclusion from phase IB.

* **Phase I trials should study diverse populations.**

Given the rough bundle of opportunistic infections and malignancies that constitutes AIDS, the idea of a homogenous HIV infected population has always been an implausible fiction. Permitting diversity among a study population will not only speed trial accrual: it will yield more widely applicable results.

New antiretrovirals should be studied in people across the entire spectrum of HIV disease and in all its different populations. A drug may have very different toxicity or efficacy characteristics at earlier stages of disease. These characteristics should be known before the drug is used in large efficacy trials and on expanded access protocols. Conducting multicenter phase I trials will provide independent confirmation of results.

* **Phase I trials should build on existing data.**

The FDA has required anti-infective drugs approved for other indications to go through time-consuming phase I trials in order to receive a new indication for AIDS. For such previously studied drugs, classic phase I trials can be abridged. Doses found safe for existing indications may be used for rapid assessment of safety and efficacy. Similarly, drugs in common usage abroad for other indications should be tested for safety in modified phase I trials, and then released for expanded access until efficacy for the new indication has been proven by a controlled trial.

* **Phase I trials need to be realistic.**

People in Phase I anti-HIV trials are often expelled from studies when they develop opportunistic infections (OIs). We now realize that the current generation of antiretrovirals does not prevent people from becoming sick. People who develop OIs during phase I studies should be able to decide to remain on the study once informed of the risk of interaction between the study drug and the treatment for the OI.

* **Women must be included in Phase 1 studies from day one of clinical testing.**

It is poor science to exclude half the species because of liability concerns and concerns for a theoretical fetus. One third of the HIV infected population worldwide is female. Are drugs being developed to treat the disease or to profit from the rapidly shrinking population of affluent PWAs (who aren't female)? If it is the former, then it is absolutely necessary to include women in early human safety and toxicity testing to document at the most research intensive point in drug development any possible differences in metabolism of an agent, as well as any women-specific side effects. To exclude women from early drug testing is to test an agent incompletely and inefficiently.

B. SPEEDING UP PHASE II/III

*** Multiple questions for single trials / Multiple trials for single subjects.**

Given the urgency of the AIDS epidemic and the many questions that need answers, no researcher conducting a large efficacy trial should be content to ask a single question.

The complexity of AIDS adds considerable difficulty to the problem of designing trials which are both ethical and scientifically productive. Hitherto many drug sponsors and investigators have ignored the best interests of the patient in order to serve an implacable methodology derived from studies of other, very different diseases.

AIDS treatments cannot be studied in isolation, because people with AIDS must take many concomitant medications. Currently, trial participants often conceal their use of off-trial drugs so as not to be expelled. More rational entry criteria would incorporate diversity; and ongoing disclosure of all concomitant medications should be encouraged. Randomization will distribute the effect of concomitant treatments among the study groups, and more information about real world interactions will be gathered.

Efficacy questions can be answered simultaneously, rather than sequentially. People can and should be able to participate in more than one clinical trial if they wish. For example, patients might choose to be in a trial of an experimental anti-HIV agent while participating in one or more studies of prophylaxis for opportunistic infections.

Protocols may be designed with nested studies that investigate questions such as drug interactions or synergies. The key is to develop flexible models that offer people with HIV maximum choice, and provide the highest standards of clinical care.

*** Efficacy trials must be flexible.**

As the course of the disease changes, study questions may also change. A protocol that fails to adapt to changes in disease patterns and state-of-the-art therapeutic management will yield inadequate answers at the end of a long, expensive study. As new anti-HIV agents emerge from phase I, trials should be flexible enough to allow for the addition or removal of one of the study drugs, changes in eligibility criteria, or different endpoints.

*** Integrate the standard of care into trials / Study standards of care.**

Trials should be oriented to finding optimal treatments for diseases rather than approving drugs. Sponsors may be reluctant to conduct such trials, but these are trials that are appropriate for a government to conduct on behalf of its people. Trials sponsored by pharmaceutical companies are oriented towards drug approval; such pivotal trials are inflexible by definition. Drug marketing approval can not be the ultimate goal of all AIDS trials.

*** Design trials that people want and need.**

It is coercive to limit expanded access in order to enhance enrollment in efficacy trials. The challenge is to design trials in which people want to participate. ACTG trial 081, a multi-modal OI prophylaxis study, is a necessary, innovative trial that people were eager to join.

* **Pregnant women must be allowed to participate in all efficacy studies.**

Trials must be designed with a contingency plan to stratify women who become pregnant while on protocol and who wish to carry to term or to abort. Animal teratogenicity studies must be initiated by the time Phase I studies have begun to show a range of active doses, or by the end of Phase I, whichever is sooner. Depending on the known and potential activities/toxicities of a drug a woman may decide to withdraw from the trial during pregnancy. If a woman makes that decision, then there must be a treatment arm for her to return to after she has given birth. If a woman leaves a trial due to pregnancy, she must be allowed to receive the study drug after the trial ends as if she had completed the protocol. Women must be allowed to receive drugs that are in FDA Pregnancy category B, and if necessary C, in clinical trials.

* **Combination efficacy trials.**

Investigators have been reluctant to draw conclusions about efficacy from the few pilot combination studies conducted to date. Preliminary results from the alternating AZT/ddC trials suggest that alternating antiretroviral therapy prolongs the efficacy and lowers the toxicity of the individual agents. Yet sponsors have done nothing to follow up on the results of these small, innovative studies. ddC has recently been released on a strictly limited program as a single agent, but its optimal use will probably be in combination or alternating use. (The ACTG has a small trial of the combination of AZT and ddC, ACTG 106. More recently, a small, privately sponsored, 5-center study of the combination of AZT and ddI opened.)

Sam Broder is conducting a 14-person study that alternates doses of AZT, ddI, and ddC weekly. This study is too small to yield data about the regimen's efficacy. Although these agents have been studied individually for years, no large efficacy trial for this regimen is on the horizon. In the meantime, some people with AIDS are combining or alternating these drugs on their own.

Sponsors may be unwilling to conduct studies of combination therapies, although they may offer the most promise. Therefore, Federally research programs must mandate such trials. The US government holds the patents on ddC and ddI (Hoffman-LaRoche and Bristol-Myers hold licenses). The government can persuade sponsors to provide drugs for combination studies.

And the government should act quickly. Once ddI and ddC are licensed, researchers may have less opportunity to conduct well-controlled studies of various combination and alternation regimens. (One ACTG investigator has gone so far as to suggest that yearly cycles of different single agents may overcome resistance to any one agent.)

* **Large Simple Trials.**

As the lag in developing combination therapy demonstrates, we need new models for conducting large scale trials during or after the period when efficacy is proven. Recently, many biostatisticians have discussed the concept of "large simple trials." A large simple trial is an efficacy trial with liberal inclusion criteria that gathers a smaller amount of data than traditional efficacy trials do. This suggestion has received considerable support from researchers, the AIDS community, and individuals within the FDA. These trials could offer thousands of people potential therapy as well as gather valuable data. The parallel track program provides the opportunity to make the idea of large simple trials a reality. See "Middle Track" below.

Decision Tree Trials

Clinical trials for **all** serious AIDS associated conditions should be available for **all** people with HIV. In this decision tree model, substantial data might be gathered while people with HIV negotiated the changing choices available to them. People would be able to enter a clinical trial at any stage of disease and choose between a standard of care arm and randomization to one or more experimental treatment arms. For example, people who are asymptomatic could choose standard therapy (AZT) for HIV, then join a trial of Imuthiol as an immunomodulator. Later on, they could join prophylaxes trials, and treatment trials if opportunistic infection occurs. Flexible allocation schemes would add new arms, randomizing at an equivalent ratio whenever new experimental agents became available for efficacy trials. A good example is the foresight exercised by the designers of the SOCA protocols, who have considered adding a new anti-CMV agent (such as FIAC or oral DHPG) to their comparative trial of foscarnet and ganciclovir, as soon as they become available.

C. HOW TO IMPROVE ALL PHASES OF TRIALS

*** Adopt rational entry criteria for clinical trials for HIV-related drugs.**

Most AIDS clinical trials exclude people who do not have certain baseline values as measured by a battery of laboratory tests. Most people with AIDS "fail" at least one. Researchers have always preferred their sick people relatively well: it's easier to measure the response to the study drug. To cling to this preference for HIV trials has made a shambles of accrual efforts, and ensures that even successfully completed trials tell sadly little about how to use a drug in the real world. HIV trials require exclusion criteria tailored to people with HIV infection. The status quo is untenable: it is utter absurdity to design trials for AIDS drugs that routinely exclude most people with AIDS.

*** Include all people with HIV Infection in trials.**

The underenrollment in clinical trials of special populations affected by HIV (such as intravenous drug-users and people of color) is slowing the research process. As the epidemic moves more and more into these populations, their underrepresentation becomes more and more severe. Equity demands that the research establishment redress this disparity, and so does practicality. Unless the research establishment reaches out to these populations, there is no hope of completing large efficacy trials quickly enough to benefit all people who are symptomatic today. The establishment must break with its standard clinical trials referral patterns that all but eliminate everyone but the patients of wealthy academic medical centers and their small circles of affiliated doctors.

*** Employ direct markers of virologic and immunologic activation in AIDS clinical trials**

Standardized, wide-scale use of new techniques like plasma viremia and polymerase chain reaction (PCR) may mitigate the interminable discussions about "surrogate" vs "direct" markers, and provide rapid means of confirming anti-HIV activity in phase I studies.

Much ado has been made about using surrogate markers in assessing the efficacy of anti-HIV drugs. Those markers which are useful are not surrogate, and those markers which are surrogate are not useful. The useful markers -- CD4 cell counts, percentages, p24 antibody and antigen levels and HIV plasma viremia -- are direct markers of immunologic or viral activation. They should be regarded as such. Methods of measuring them should be standardized, research labs accredited, and efficacy trials may be greatly shortened. If a new compound affects these markers (for example, causing a rapid and sustained drop in HIV plasma viremia), it could rapidly be distributed through Parallel Track, while

efficacy trials far smaller than currently conducted could assess long-term outcomes and the safety of chronic therapy.

* **The rights of trial participants to continued therapy.**

Subjects put their bodies on the line. Yet too often their access to the study drug is cut off at the end of the study period. Pharmaceutical companies should acknowledge the contribution of participants in clinical trials. People who take part in clinical trials must be guaranteed a supply of the study drug should they wish to continue taking it. The rights of people who are willing to assume the risks of early drug research must supersede the narrow financial interests of sponsors. Guaranteeing continued therapy will likely have the subsidiary benefit of improving trial accrual.

* **Participation of community members in clinical trial design.**

The communities affected by AIDS must be involved in protocol design, to ensure that the clinical trials that are conducted are necessary and practical. In addition, large efficacy trials require the collaboration of many members of the various communities affected by the disease in order to be successful. Including community members in protocol design will foster such cooperation.

* **Develop methods of testing other, non-pharmaceutical treatment modalities.**

There are treatment modalities which are systematically excluded from government, industry and university sponsored clinical trials. Some of these approaches, such as traditional Chinese medicine, have been used for thousands of years. In such cases, phase 1 trials should be abridged, incorporating known data. In some cases, there are preliminary indications of efficacy derived from treatment uses abroad; these should become the basis for systematic clinical research in the USA. Among these approaches are traditional African herbology, Chinese medicine, homeopathy, macrobiotics and other nutritional regimens, Indian Ayurvedic medicine, and vitamin and mineral-based therapies.

D. NOTES TOWARD A PEDIATRIC TREATMENT AGENDA

Minors are typically excluded from clinical trials as a matter of course. The reason most often cited is concern for the safety of the child. Experimental drugs do not have well characterized toxicity profiles. The assumption here is that toxicity data gleaned from adult trials will figure in the construction of pediatric protocols, that somehow, if we understood the drug's toxicities in adults more completely, we'd be better able to deal with toxicities in children.

The idea of letting adults assume the risks in toxicity studies, to protect children, is obviously appealing. Unfortunately, the "truths" upon which this idea is based are philosophical rather than scientific. Toxicity data yielded by phase II and III trials in adults does not have significant bearing on the way pediatric studies are designed and implemented.

Phase II/III trials survey for toxicity, rather than closely defining it. They are designed to answer extremely broad questions, characterizing the responses of populations rather than those of individuals. Such trials quantify the likelihood of various adverse reactions, but provide precious little in the way of guidance for optimizing individual therapy, or managing toxicities. The severity, duration and frequency of the reported side effects, how they were discovered, and the value of different approaches to their medical management are seldom discussed in journal articles.

Many drugs are effective at much lower doses in children than in adults. Dose/response relationships are often different for children. Since these relationships are elicited in phase I pharmacokinetic studies, this is the time and place to learn how to protect children from toxicities.

Toxicity issues impact differently on children than on adults. While adults may be willing to endure periods of drug-related discomfort if they perceive long-term benefits, children are often less willing to tolerate such discomfort.

HIV infection is briefer and more acute in children than in adults; hence valuable efficacy data can often be gathered faster in pediatric populations. Phil Pizzo's studies of AZT in children with HIV provide some of the most compelling data on AZT's antiretroviral activity and its ability to restore neurological and cognitive functions.

Simultaneous implementation of phase I pediatric and phase II adult trials will facilitate the development of unbiased pediatric results. Toxicity data are particularly vulnerable to the effects of bias. If a drug is purported to be nontoxic in adults, this could bias pediatric investigators to discount side effects reported by their subjects even more than they do now.

More children have already suffered and died due to untreated HIV infection than will ever die of drug reactions. Waiting until adult efficacy studies are completed before initiating pediatric studies endangers more children than it protects. Regulators and investigators often deal with the fact that HIV infection is lethal to children as if this issue were only peripherally relevant.

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IV. PARALLEL TRACK + a Proposal for a "Middle Track"

A. Parallel track

One of the few bright spots in a depressing year for AIDS treatment research was the genesis of the Parallel Track and its development by an unprecedented cooperative effort between activists, researchers and regulators. First proposed by Jim Eigo in April 1988, and subsequently brought to public attention by Anthony Fauci in spring 1989, Parallel Track had its roots in the prolonged and agonizing DHPG approval process.

DHPG (ganciclovir), the first drug with powerful anti-CMV activity, was first synthesized by 4 rival teams in 1982. Until then, there had been no treatment effective against CMV retinitis or colitis, which led to blindness and wasting, respectively. Subsequently, a patent battle ensued between Syntex and Burroughs-Wellcome. Uncertainty over the result led Syntex to neglect to conduct well-controlled clinical trials, but the company did distribute the drug to thousands of people with CMV retinitis under an FDA approved compassionate use ("single patient") IND. In November 1987 the FDA Anti-Infective Drugs Advisory Committee, not yet sensitized to the realities of AIDS, voted not to recommend approval, in spite of the objections of its two ophthalmologists.

Compassionate use distribution continued through the end of 1988, when, in an effort to force people into a delayed treatment controlled trial, NIAID and the FDA restricted access to the drug. A widespread outcry culminated on February 1, 1989 in an ACT UP demonstration at a speech given by Ellen Cooper of the FDA. That day, 3 ACT UP members met with Fauci, who promised to intervene with FDA to restore compassionate use access. Three weeks later, the FDA relented, and in June, despite the lack of data from controlled trials, FDA approved the drug for marketing.

Throughout those months, Fauci maintained that Syntex's mistake had not been distributing the drug, but failing to conduct proper studies concurrently.

The solution, Parallel Track, was designed to provide access to a new drug with proven safety for people intolerant of standard therapy and unable to enter clinical trials of alternatives.

ACT UP spearheaded an effort to develop guidelines for Parallel Track, and these were endorsed by 20 AIDS groups and the FDA Anti-Viral Drugs Advisory Committee on August 17, 1989. The National AIDS Program Office (NAPO) then convened a task force, including members of ACT UP and Project Inform, to draw up detailed recommendations.

The Pharmaceutical Manufacturers Association, in spite of years of deregulatory fervor in Washington, was unduly worried by the implications of Parallel Track, citing tired concerns about liability and cost, and significantly delaying implementation.

After a tortuous progress through the byzantine Health & Human Services bureaucracy, the Parallel Track regulations were published as a proposed rule in the Federal Register on May 21, 1990.

Under the rule, candidate drugs for Parallel Track will be eligible after completing phase I trials, showing acceptable safety and suggestions of activity. The AIDS Research Advisory Committee (ARAC), mandated by the Health Omnibus Programs Extension (HOPE) legislation of 1988, is empowered to recommend a drug for Parallel Track. This panel, however, has not yet met, halfway through its two-year term.

Ultimately, it will be up to FDA to approve a drug for Parallel Track, but community input will be heard at the ARAC level. The proposed rule also contains guidelines for removal of a drug from Parallel Track, should the drug prove too toxic, should efficacy trials conclude the drug doesn't work, or should expanded access impede the controlled trials.

Simultaneously with the bureaucratic travails of the official Parallel Track, a prototype was being carried out with ddl. Last year in Montreal, we called for "an end to the quarantine of the AZT intolerant." We feared that the imminent efficacy trials of ddl, which would compare it to AZT, would deny the 50% of people intolerant to AZT any chance for alternative therapy. Much to our surprise, FDA, NIAID and Bristol-Myers were all receptive to the idea of expanded access to ddl for people intolerant of AZT and unable to participate in ACTG 118, the dose comparison trial of ddl.

In October 1989, ddl became available to AZT intolerant persons on a treatment IND, and to AZT failures on an open label safety study. These two protocols used existing (and often, previously, underutilized) FDA mechanisms for providing access to an unapproved drug. By June 1990 these programs had enrolled over 9,000 people with AIDS, more than any other AIDS related expanded access program. This represented a triumph for activism, and a breakthrough to reasonable behavior for researchers and regulators.

As a trial run, the ddl experience has taught much about the value, as well as the potential pitfalls, of Parallel Track.

Because the designated investigators were busy writing up their AZT results last fall, they did not focus on the ddl protocols until the studies were already written by Bristol-Myers and FDA. Changes in dose, formulation, and study designs led to delays at the individual sites, as institutional review boards (IRBs) insisted on approving all changes. Hence the expanded access studies opened before the controlled trials in many areas.

Moreover, many sites lacked staff to screen everyone on their waiting lists. Some people got tired of waiting and signed up through Parallel Track. Absurdly narrow (and in some cases anachronistic¹⁸) entry criteria led to unnecessarily slow accrual. Of the first 150 potential subjects screened at Memorial Sloan-Kettering in New York, only 3 were eligible.

At the same time, some investigators screamed that expanded access was ruining their clinical trials. Yet easily avoidable bureaucratic and methodologic errors accounted for most of the disparity. This didn't prevent some -- such as Douglas Richman of UC San Diego -- from claiming that "Parallel Track, as conceived and implemented, is a disaster."

The truth is that Parallel Track will not, itself, improve clinical trials. It will only mitigate the slowness of the research system. If it is to succeed, the controlled trials to which it is parallel must be designed to be as attractive as possible, and relevant to the real world.

Other investigators, after initially opposing Parallel Track, came to support it. These include Martin S. Hirsch of Harvard and Paul Volberding of UC San Francisco.

Criticism of the program recurred in March, however, after an ACTG investigator opposed to Parallel Track seems to have leaked the number of deaths on expanded access to a reporter. The subsequent news story spread panic among people with AIDS, and heartened the methodologists who demand that gathering data must precede access.

While the suggestions for a "Middle Track" listed below may quell the concerns of these methodologists, it is important to note that the primary intent of Parallel Track is to provide access to potential treatment for people who lack alternatives, not to gather efficacy data for a drug sponsor and the FDA.

The Parallel Track is still not a reality. Too few drugs have reached the stage where they are eligible, and too few of those are promising. The ARAC must schedule quarterly meetings, beginning this summer. And pharmaceutical sponsors must show that they are willing to participate in this new endeavor.

B. "Middle Track"

By March 1990, 290 of 8,000 people enrolled in the expanded access program for ddI had died. At the same time, less than 10 people had died in the phase II trials (N = 790, at that time). Opponents of Parallel Track used this in their ongoing campaign. Yet the two groups were not comparable: expanded access was designed for a population with more advanced AIDS; only 6 of the deaths on expanded access could be associated with ddI related pancreatitis.

Nonetheless, it has recently become clear that the doses of ddI now being studied, like those of AZT and ddC before it, are probably too high. Even the lowest doses studied in the ACTG phase I trials were active against HIV. And because some of ddI's toxicities -- such as peripheral neuropathy -- are clearly dose related, it is desirable to ascertain, as quickly as possible, the lowest effective dose of ddI.

¹⁸ ACTG 116 compares AZT and ddI in people with advanced ARC or AIDS who have never taken AZT. Because of the recent expansion of AZT's indication to people with under 500 T cells, and because many people with HIV were taking it before this expansion, the population most accessible to this trial contains few "AZT virgins." The inclusion criteria should be expanded to include people with fewer than 500 T cells.

If Parallel Track had been implemented with an optional efficacy component (here dubbed "**Middle Track**"), people enrolling at sites capable of collecting more detailed -- but still minimal -- efficacy data could participate in a randomized form of Parallel Track which would compare various doses of the Parallel Track drug, and generate rapid efficacy data. (For example, with ddl, if mortality were measured in expanded access, and different doses used, we might have learned a lot more about ddl's usefulness in the real world). Sites appropriate for Middle Track would include community-based clinical trial groups and qualified physicians' offices and public health clinics.

Such a Middle Track would add a minor administrative cost to a sponsor's expenses for participating in Parallel Track, but it would yield a gold mine of real world efficacy data. This trade off seems potentially valuable, as long as the Parallel Track were still available through clinics and doctors who could not afford the extra data collection activities.

In other words, Middle Track would, like Parallel Track, be primarily a distribution program, with a secondary goal of gathering minimal efficacy data. The endpoints could be similar to those used in large simple trials.

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V. ACTIVIST MANDATES

A. To President Bush and the US Congress.

This year AIDS research funding isn't even keeping up with inflation - it's due to rise about 7%; the AIDS caseload will double, to 200,000. Double the entire NIH biomedical research budget. Restore funding for 50% of grants deemed worthy of funding, as occurred in the 1970s. Stop pitting people with different diseases against each other. Involve people with different diseases in research on those diseases. Speed up patent review of new treatments. Extend Medicaid coverage to all Americans lacking health insurance. Mandate states to cover AIDS therapies, including off-label uses. Mandate insurance companies to cover off-label uses of approved therapies, and to contribute towards medical costs associated with participation in clinical trials. Guarantee health care to all Americans. Remove INS restrictions on the travel of HIV infected persons in and out of the USA. Stop HIV testing for immigrants. Provide leadership and insist on accountability and rapid progress against AIDS and all other serious and fatal diseases. Fund and implement the 1989 PHS guidelines on monitoring and early intervention for HIV infection, including free periodic T cell testing, early antiretroviral therapy and PCP prophylaxis. Get the FDA some computers and a new campus. Raise NIH salaries to make them competitive with those of industry. Demand a conflict-of-interest policy mandating full disclosure of all ties with industry for investigators receiving government funds.

B. Blueprint for a More Productive A.C.T.G.

On May 21, ACT UP stormed the NIH to demand a more efficient, humane research enterprise. Most of those involved in AIDS research, whether at NIH or in the academic sites funded by the ACTG, are talented and dedicated professionals. Yet the structure of the ACTG system denies them the chance to work to their full abilities, and, in its first five years, the ACTG has been a dismal failure.

Next year, the second five-year round of ACTG grants will be awarded. In the first five years, the landscape of AIDS has been utterly transformed by treatment advances, most of them developed outside the ACTG. Yet the \$100 million annually awarded to this program can be used better, and should not be scrapped. In its next phase, the ACTG has the opportunity to learn from its mistakes, incorporating new developments in treatment and in clinical trial design, and to open the process to people with AIDS and activists at every level.

In discussions with investigators over the past months, it has become clear that many talented researchers are not satisfied with the system, and do most of their constructive work outside of it. This is because ACTG research priorities are set in private by a small number of principal investigators who sit on the Executive and Primary Infection Committees, in conjunction with NIAID's Division of AIDS. Hence the emphasis on nucleoside analogue antiretrovirals, tested to the exclusion of many other approaches. The original ATEU system was divided into part A (HIV research) and part B (opportunistic infections and cancers). Some have suggested that the ACTG be decentralized, that it continue conducting multicenter trials of anti-HIV drugs, and that individual sites compete for a new form of the old part B contracts, so that investigators can pursue their interests with the guarantee that they will be able to implement their proposed studies. In other words, the present cooperative agreement system would continue for large phase II/III trials, while targeted research contracts would be issued for the major opportunistic infections and cancers, and for small phase I/II studies.

There is a precedent for this decentralized approach in the SOCA (Study of the Ocular Complications of AIDS) program, which will use ACTG sites and others to compare DHPG vs Foscarnet in treating CMV

retinitis. The design is flexible, to allow incorporation of new anti-CMV therapies as they become available. Expert ophthalmologists and trial designers are collaborating with people from the AIDS community on this project.

It is not clear at this point whether the best approach to structuring AIDS treatment research would lie in more decentralization, with targeted contracts to ensure that all major areas were addressed, or simply in a restructuring of the ACTG in its second five years. Should the program continue in something like its present form, we recommend the following changes:

Changes in the ACTG structure. The ACTG is controlled by its Executive Committee (EC), acting in concert with NIAID's Division of AIDS. The EC selects the chairs of each research committee¹⁹, and the chair in turn selects the core research committee members, who make all important decisions in private, as does the EC. Hence the program is directed from the top down. Investigator-initiated concept sheets are filtered up through the appropriate research committee, but the EC makes all final decisions. This leads to frustration for investigators whose trials are never approved, or, once approved, subsequently placed on hold. The Opportunistic Infections (OI) Committee, for example, has Pathogen Study Groups (PSGs) for each major OI. These PSGs have had studies designed and ready to go for several years, but most are never implemented.

The entire research committee should select its core committee, which should select its chair. In addition, the core committees should elect delegates to the Executive Committee, and each committee should be represented equally there. People with AIDS and activists should have full voting powers on all core committees and on the Executive Committee. Meetings should be conducted openly, with executive sessions only when a drug sponsor is presenting preliminary data.

Changes in the ACTG's research priorities. Now, virtually any complaint about the ACTG system is rebuffed with a pious invocation of the "priority setting process." This is a process to which few have entree, and even fewer influence.

The ACTG should set its priorities in an open fashion, after a debate of its entire membership, including input from people with AIDS and activists. Resources should be divided among each research committee in proportion to how much of the overall AIDS problem lies in that committee's bailiwick. Thus, perhaps half of adult trials and half of pediatric trials could focus on primary (HIV) infection. The other half could be divided between the opportunistic infections and cancers, neurology and other complications. Within both areas, a significant proportion of the research effort should focus on phase I trials of new compounds. In addition, there is no reason not to consider innovative studies designed to enhance trial accrual and compliance, and quality of life.²⁰

Currently, many drug companies have become reluctant to submit new agents to the ACTG. The February meeting of its drug selection committee²¹ was cancelled for lack of submissions. If sponsors are unwilling to use the system, the ACTG will continue to founder. If sponsors are to be brought in,

¹⁹ The ACTG has 8 research committees -- Data Management, Neurology, Oncology, Opportunistic Infections, Patient Care, Pediatrics, Pharmacology, Primary Infection -- and two resource committees, Immunology and Virology. The Immunology Committee has a working group devoted to immune-based therapies, replacing the Biological Response Modifiers Committee, which bowed out in 1989.

²⁰ The Patient Care Committee proposed ACTG 126, "Impediments to Accrual of IV Drug Users in ACTG Trials," but this initiative was cancelled by the EC in March.

²¹ The AIDS Clinical Drug Development Committee (ACDDC), technically an independent advisory body reporting to Fauci, but loaded with Division of AIDS staff, Executive and Primary Infection Committee members.

the ACTG must provide a means of guaranteeing rapid accrual into its studies, timely completion, and efficient analysis and publication of results.

When NIAID interrupted ACTGs 016 and 019, it distributed a "Letter to Physicians" around the country. Many doctors, however, are reluctant to practice medicine by press release. Alternatives to waiting for peer reviewed publication in medical journals must be developed, to speed the transfer of trial results into everyday clinical practice around the country. NIAID should consider a quarterly newsletter of research results, and must establish an Office of Patient Care to oversee the translation of data into guidelines for clinical practice.

The ACTG should also establish a committee to deal specifically with HIV disease as it manifests itself in women. Women can no longer be considered solely under the rubric of the Pediatric Committee, as they are now. Such a program would incorporate the existing Obstetrics & Gynecology Working Group, and would provide primary care to all participants who would otherwise be ineligible for lack of health care.

Changes in ACTU sites. Funding for each AIDS Clinical Trials Unit (ACTU) must be tied to performance. Sites which consistently lag should be cut off, and new sites established in areas with high HIV incidence and competent researchers. There are other impediments to accrual, however, which only the central program can resolve. The present system prioritizes trials, rewarding those who enroll large numbers in high priorities, and penalizing those who focus too much on low priority studies. All implemented protocols should be considered high priority. In addition, many trials have foundered because of poor design, or irrelevance to the needs of people with AIDS.

To mitigate all these problems, each ACTU should establish a community advisory panel to provide input on the relevance of studies, improvements in trial design, and advice on conducting outreach to the diverse affected communities.

In addition, the ACTUs need to improve communication within hospital sites. Today, many eligible participants are never screened because emergency room staff (for example) don't know about trials going on upstairs. ACTUs must have a plan to coordinate information with nearby health care institutions to enhance enrollment, and within their own institutions.

The ACTUs must enhance services to potential and real participants. Many people need transportation subsidies, and some need child care if they are to participate in an ACTG trial. These must be provided. Too often, participants are now abandoned once the trial is over. A more humane model would provide continuing HIV care for all those who have offered their bodies for science. This might enable more rapid enrollment of follow-up trials.

Those who care for participants and manage the data -- largely unrecognized, underpaid and female -- have insights into research which should be taken into account by those designing trials, and those who take the credit. State-of-the-art standards of care for people with HIV, in and out of trials, must be observed at all ACTUs.

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C. Suggestions for AIDS Activists

- * **Get Involved In your local ACTU (AIDS Clinical Trial Unit).** All ACTUs need to have community advisory panels. A community advisory panel can help set research priorities, evaluate protocols, and make sure that the all affected communities are represented in clinical trials. Your ACTU may not willingly receive your input, but you must demand to be heard. Trials done without community input and support are likely to be outdated and irrelevant, or poorly designed. If your community does not have an ACTU advisory panel, you must fight for one.
- * **Get involved in your local Community-based research organization.** Community based research organizations need the same input that ACTUs do. If your community does not have a community based research organization, think about starting one.
- * **Adopt a Principal Investigator.** It is essential that AIDS activists become experts at the research going on in their communities. Meet the PIs conducting trials. Read their papers. Read their protocols. Discuss their research with them and their staff. Their staff is often more candid. Find out what they researched before AIDS. Learn their consultancy arrangements. Any scientist is influenced by received dogma and industry alliances. Challenge them to make sure that these things are not biasing their research.
- * **Have a teach-in in your community.** Knowledge is our key to fighting the HIV epidemic and the HIV bureaucracy. Scientists often discount activist input, claiming we lack their experience and expertise. This is not true. Activists have made themselves experts. We must share this expertise.
- * **Adopt a drug.** Many drugs seem to get lost or waylaid between discovery and approval. Studies are indefinitely delayed and people with HIV are denied access to drugs. We must be vigilant to prevent this from happening. Identify a drug you think is languishing and contact the company that produces it and the FDA officer who monitors its approval process. Find out sources of delay and seek to overcome them through letter-writing, phone calls, or direct action. Other activists from around the country are monitoring the same drugs; find out who they are and join forces for a national effort to assure speedy approval and distribution.
- * **Communicate what you learn.** Share any knowledge that you gain with other activists and the public. Translate what you learn into language that is appropriate for the evening news. Hold events and demonstrations that allow you to communicate what you have learned through the media.
- * **Reading is fundamental.** Get ahold of the latest scientific journals. Start a science club to discuss important articles and share what you learn. Attend scientific meetings in your community and represent your point of view.

* * *

This document is a collaborative project of the Treatment + Data Committee of ACT UP/New York. Contributors include Matthew Burns, Jim Eigo, Ken Fomataro, Garance Franke-Ruta, Mark Harrington, Bob Huff, Cassandra Freedom-Jones and Rich Lynn.

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ACT UP

Treatment & Data Committee, New York

AIDS Treatment Research Agenda

**VI International Conference on AIDS
San Francisco**

June 1990

TREATMENT AGENDA 1990

ACT UP / New York

Treatment + Data Committee

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- VI "International" Conference on AIDS -
San Francisco
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I. INTRODUCTION: Science in a Crisis

We have lost the war against AIDS. Millions who need not die so young will die so young... Even if a cure were found tomorrow, the system would not test and make it available fast enough to save us.

- Larry Kramer¹

The problem of AIDS is still with us.
We still have not achieved cure.

- Daniel F. Hoth
Director, Division of AIDS
NIAID, NIH²

We are all dying.

- Tofa, a 26-year old man
Uganda³

*

In the tenth year of an epidemic which may be with us all our lives and end some of them, the remaining forces are gathering in one of the cities where it first appeared. Three ghostly entities will face each other at the Moscone Center in San Francisco when the Sixth "International" Conference on AIDS opens Wednesday afternoon: the absence of George Bush, whose silence equals our deaths; the absence of researchers who never went after AIDS because there were no research funds; and the absence of 80,000 Americans (and hundreds of thousands of people around the world) murdered by the ghastly alliance between a tiny piece of fucked up data (HIV) and a huge, indifferent bureaucracy (the US government).

After several years of AZT and precious little else in the developed world, and after 10 years of virtually no treatment in the third world⁴, people affected by AIDS worldwide are waking to the recognition that the countries with the resources to end the epidemic -- chiefly the USA -- have no intention of taking the necessary steps. Next year's AIDS budget is smaller than that for the space station "Freedom"⁵. And yet President Bush claims we are "on a wartime footing at the National Institutes of Health. Slashing red tape. Accelerating research. Boosting the budget."⁶

¹ At the second Michael Hirsch awards, New York, 5.90.

² May 15, 1990

³ Jane Perlez, New York Times, 6.10.90, A14.

⁴ Uganda, where in some cities one in four is seropositive, spends but \$1.00 per capita on health care each year.

⁵ US AIDS research budget: \$1.7 billion. NASA space station budget: \$1.8 billion. William J. Broad, New York Times, 6.10.90, p. A30.

⁶ President Bush's first speech on AIDS, 14 months into his term of office.

It's time for a Manhattan Project against AIDS, with a mandate from the highest levels of the US government and endowed with whatever resources it takes to get the job done.

The likelihood of this happening is virtually nil.

Among the communities affected by the disease, prolonged exposure to its realities is provoking not denial but despair and desperation. This year, the hopes of many in the AIDS communities have reached a low ebb. It is clear to all that anti-HIV agents such as AZT, ddC and ddI will not, in any conceivable combination, stop the progression of HIV infection -- at most, for those who are lucky, they will significantly slow it.

At the same time, no new anti-HIV agents have emerged from phase I studies ready for wide-scale trials. This is largely because there have been few phase I studies of new anti-HIV drugs over the past year. New drugs by the dozen are emerging from laboratories around the world, but those in charge of the US AIDS research effort have chosen to focus on conducting wide-scale post-marketing studies of existing treatments (chiefly AZT), while virtually ignoring most of these new approaches.

This must change. Without a commitment to developing new anti-HIV agents from the test tube through phase I/II studies, as well as significantly expanding the scope of opportunistic infection prophylaxis and treatment, and cancer treatment, the US AIDS establishment is abandoning hundreds of thousands of people with HIV to a world of impoverished therapeutic alternatives.

Even those therapies which have become available over the past year -- e.g., aerosolized pentamidine, DHPG, fluconazole, and (for some) ddI and EPO -- are unavailable to most of the people who need them. The government has done nothing to implement last year's PHS recommendations on monitoring HIV infected people to provide early antiretroviral intervention and prophylaxis against PCP when needed. Hence, pneumocystis is still the most common AIDS-defining event.

In spite of the overwhelmingly bleak reality which surrounds us as the AIDS epidemic enters its second decade, there are some new alliances which are worth noting:

- Activists worked with NIH researchers and the FDA to design the "Parallel Track" program for systematizing expanded access to certain new therapies, and then with Bristol Meyers to design the ddI expanded access protocols; such coordination and cooperation must become the rule, rather than the exception.
- Activists are working with community-based clinicians, NIH biostatisticians and researchers on the design of the Multiple Opportunistic infection Prophylaxis (MOPS) study for the Community-Based Clinical Trials Network (CBCTN) and the SOCA (Study of the Ocular Complications AIDS) trial of DHPG vs Foscarnet in CMV retinitis. NIH biostatisticians established the Statistical Working Group (SWG) within the ACTG to provide a forum where activists, researchers and statisticians can work together to streamline old studies and create innovative new models for clinical research.
- After ACT UP struggled with NIAID Division of AIDS officials to attend ACTG meetings, the NIAID established a Patient Constituency Working Group (PCWG) to represent people with HIV and affected communities within the ACTG; subsequently, the ACTG Executive Committee recommended that each ACTU establish a community advisory panel. This should be the model for all AIDS trial sites, community-based and academic.

The following three objectives will define the core arena for AIDS treatment activism in the coming year:

- * **Broadened research priorities**
- * **Innovative clinical trial designs**
- * **Vastly expanded health care and treatment access**

One year ago in Montreal, ACT UP proposed its National AIDS Treatment Research Agenda. The most tangible result was the expanded access program for ddI, which enabled 10,000 Americans to receive this potential therapy in a prototype for Parallel Track. At the same time, however, and more deeply felt in the communities affected by AIDS, was the loss of tens of thousands of people, and new diagnoses for tens of thousands more.

AIDS is causing an abrupt and seismic shift in biomedical research. The outlines of a new research order are emerging. Some scientists are changing, adapting to this new order. History will record the names of those who assist in creating a more equitable, humane and efficient research system, and it will record the names of those who resist. It is time to make one thing clear: people with AIDS will win this battle. Science will serve their needs. Either scientists will work with us in advocating change, or they will be forced to step aside. It is time for activists from around the world to make research accountable to the needs of people, not profit.

There is only so much horror a people can tolerate. Again, this year, we propose the elements of a rational, comprehensive and coordinated research effort to systematically target all the serious and fatal complications of HIV disease. If our message is not heeded within the coming year, the rapidly diminishing hopes of our communities will vanish. What will happen then?

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II. DISEASES + DRUGS TO STUDY

A. Research Priorities Revisited

* HIV and the Human Immune System

Virology as a clinical science is still embryonic. The first 10 years of HIV research have been based on models derived from DNA viruses like herpes simplex. Thus, Burroughs-Wellcome, developer of the HSV DNA chain terminator Acyclovir, applied this technique against HIV with AZT. Eventually it became clear that dideoxynucleoside analogues have only limited efficacy in HIV disease. New pathogenetic explorations and clinical approaches are needed. They are not being explored.

During the era of AIDS, great strides have been made in virology and immunology. Yet even those investigators who have found intriguing laboratory results have not yet applied these insights to treatment research.

For example, work carried out in the Laboratory of Immunoregulation at the NIAID has shown that herpesviruses, including HSV, CMV and EBV, accelerate HIV production by stimulating tumor necrosis factor (TNF), which, in turn, stimulates HIV. This "positive feedback loop" may contribute to the wasting (cachexia) and anemia associated with AIDS.

The obvious clinical corollary would be initiation of anti-HSV therapy as soon as HIV infection was diagnosed. Long before HSV or CMV infections become clinical, they may be assisting HIV in its

subversive assault on the immune system. Yet no studies have been undertaken of acyclovir, for example, in asymptomatic HIV infection. Many people with HIV are taking the drug on their own.

For several years, prevailing dogma held that HIV, and HIV alone, led to AIDS. Now, many of the once most ardent defenders of the "HIV is necessary and sufficient" dogma have reversed their views, and a wild hunt is on for the various co-factors -- other pathogens and native human proteins -- which may accelerate HIV-associated immunosuppression and its complications.

Theories of Viral and Cytokine Co-Factors for AIDS

<u>Proponent</u>	<u>Viral Cofactor</u>	<u>Cytokine Cofactor</u>	<u>Postulated Effect</u>	<u>Year Proposed</u>
Sonnabend		IFN-alpha	AIDS	1982
Sonnabend	CMV, HSV		AIDS	1983
Fauci	CMV, HSV		Synergistic w/ HIV	1988
Fauci		TNF-alpha	AIDS; cachexia, anemia	1989
Gallo	HTLV-I		AIDS	1982
Gallo	HTLV-IIIb		AIDS	1984
Gallo	HHV-6		Synergistic w/ HIV (?)	1989
Gallo		FGF, PDGF	KS	1990
Miles		IL6, TGF-beta	KS	1990

Viral cofactors: CMV = cytomegalovirus; HSV = herpes simplex virus (1-2); HTLV = human T cell leukemia (or, once, lymphotropic) virus; HHV = human herpes virus. Cytokine cofactors: IFN = interferon; TNF = tumor necrosis factor; FGF = fibroblast growth factor; PDGF = platelet-derived growth factor; IL6 = interleukin-6; TGF = transforming growth factor.

Joseph Sonnabend first noted the unusual presence of circulating alpha interferon in the blood of people with AIDS in 1982. This insight was ignored in the mad rush to "zap the virus" once it was discovered, and in the late 1980s when cofactors became the rage, Sonnabend's contributions were not acknowledged.

Some investigators have proposed attempting to control obvious abnormalities associated with AIDS, even in the absence of a complete understanding of their etiology, as a therapeutic strategy. Others propose using the very cytokines found in abnormal quantities. This leads to the paradoxical situation we are in, where some advocate using anti-interferon antibodies, and others prescribe recombinant alpha interferon as treatment. Similarly, Genentech is testing recombinant tumor necrosis factor while NIH investigators are proposing anti-TNF antibodies. Perhaps head-to-head comparisons of "therapeutic" cytokines against their "therapeutic" antibodies might resolve this dilemma.

It is quite possible that some of these abnormal growth factors may represent the body's attempt to fight off the effects of HIV. Circulating interferon, for example, might be a vain attempt to mobilize the body's antiviral defenses. Perhaps this accounts for the purported anti-HIV effects of interferon when administered earlier in infection.

Similarly, some of the growth factors recently proposed as elements in the pathogenesis of Kaposi's sarcoma -- e.g., FGF, TGF-beta, IL-6 -- might be produced to inhibit HIV, but have the untoward effect of accelerating the virulence of KS. Hence, antagonizing them with treatments might vanquish the KS, but accelerate the HIV disease process. Recently, it has been proposed that herpes viruses gain entry into cells by 'hitching a ride' on fibroblast growth factor (FGF).⁷ Perhaps, if this is so, this provides yet another mechanism for HSV-associated TNF and KS-associated FGF to accelerate HIV disease.

⁷ DP Hajjar, Science, 6.15.90.

In the absence of a convincing global explanation for HIV's pathogenicity, it is imperative that diverse hypotheses be examined, both in the laboratory and in humans. It is evident that the dogmas of single agent therapy are outdated.

New approaches should be based on how the actual disease (as currently manifested) presents itself clinically, rather than on perspectives derived from the primitive antiviral work which preceded it. We still cannot cure any viral disease. Approved agents (Acyclovir, AZT) are only virustatic, not virucidal. Thus, retroviral theoreticians must descend from their ivory towers to intervene on each of the clinical complications of AIDS to make real progress.

* Opportunistic Infections and Cancers

All too often, the opportunistic complications of HIV infection have been regarded as mere "noise" distracting from the underlying HIV "signal." People with AIDS have been forbidden OI medications or thrown off anti-HIV drug trials when they developed such complications. This metaphysical preference for using mediocre anti-HIV drugs and forbidding effective anti-OI prophylaxis and treatment led to much unnecessary sickness and death.

ACT UP's call to make the major AIDS-associated opportunistic infections preventable by 1991 seems to have fallen on deaf ears. The last year has seen an increase in plans to conduct prophylaxis trials, but few have gotten off the ground.

Pneumocystis carinii. PCP remains the leading OI at AIDS diagnosis⁸, in spite of the development of effective prophylaxis. The US government remains unwilling to subsidize the nationwide screening and prophylaxis necessary to make PCP a thing of the past. This is genocide by indifference. If this pattern continues, at least 260,000 new cases of PCP may occur by the end of 1993.⁹ A day in the hospital with PCP costs more than a year of aerosolized pentamidine prophylaxis; Bactrim and Dapsone are even cheaper than this overpriced LyphoMed orphan drug.

Other troubling research questions are coming to the fore: 1) PCP breakthrough in spite of prophylaxis (which seems to be on the increase, especially for people on aerosolized pentamidine), 2) diagnosis and treatment of extrapulmonary pneumocystosis in people on aerosolized pentamidine, 3) adoption of guidelines for prophylaxis in children with HIV, 4) how to revive the ACTG's stalled studies of trimetrexate for treatment of refractory PCP, 5) what is the best dose and nebulizer for optimizing use of aerosolized pentamidine, and 6) is daily systemic PCP prophylaxis with Bactrim or Dapsone better or worse than intermittent dosing. DFMO (eflornithine) is another promising agent lost in development. Burroughs-Wellcome has a new compound, 566C80, which kills the pneumocystis organism and is non-toxic, at least in early human trials.

One ACTG study, 081, compares three anti-pneumocystis agents to see which provides the best protection against PCP, and whether local (aerosolized pentamidine) or systemic (Bactrim or Dapsone) prophylaxis is most useful. It enrolled its target 450 subjects in record time, and recently expanded accrual to 600. A nested study of Fluconazole vs Clotrimazole for fungal prophylaxis (ACTG 981) enrolled equally fast. This shows that the ACTG can enroll subjects quickly in a well-designed, clinically relevant OI prophylaxis trial. Its task now should be to expand prophylaxis studies to CMV, MAI and toxoplasmosis.

⁸ Lawrence K. Altman, New York Times, 6.12.90.

⁹ PHS estimate of total AIDS caseload by end of 1993: 400,000 -- including 260,000 new cases. Without prophylaxis, PCP occurs at AIDS diagnosis in 60% of cases and eventually in 80%.

Cytomegalovirus (CMV) treatments remain highly toxic and invasive. Between 10-25% of PWAs develop disseminated CMV infections (26,000-65,000 cases by 1993). Evidence from Fauci's lab and others indicates even subclinical CMV can accelerate the progression of HIV disease. Five steps, then, are essential: 1) immediate FDA approval of **Foscarnet**; 2) study of anti-CMV medication as a form of "cofactor control" in asymptomatic populations; 3) study of oral anti-CMV agents for prophylaxis of disseminated disease; 4) development of oral anti-CMV agents for treatment, to obviate the need for dangerous catheters; and 5) FDA approval of **DHPG** for CMV colitis and other disseminated forms of CMV disease. Drugs to watch out for: **HPMPC**, **PMEA**.

Toxoplasmosis. Some researchers estimate 30% of the HIV infected population overall is positive for antibodies to *Toxoplasma gondii*. Of those infected, about 1/3 go on to develop toxoplasmic encephalitis. If 10% of all people with AIDS are at risk for toxoplasmosis, there may be 32,000 cases by the end of 1993. The ACTG has opened one trial for treatment of toxoplasmosis (**pyrimethamine/sulfadiazine** vs **pyrimethamine/clindamycin**); it has enrolled at a snail's pace (1 person every 2 months) for a total of 3 subjects.¹⁰ Community-based clinical trial sites have been discussing several toxoplasmosis prophylaxis protocols for over a year now; they should stop taking and start the studies.

Mycobacterium avium complex (MAC, a.k.a. MAI) affects between 50-75% of people with advanced AIDS¹¹ (> 130,000 cases by 1993). The ACTG has yet to open a single trial for treatment of this chronic wasting disease, although one is on the drawing board. Pharmaceutical sponsor **Adria** despaired of the ACTG and is conducting its trial of **rifabutin** (ansamycin) for MAC prophylaxis through community based research groups. New macrolides such as **clarithromycin** and **azithromycin** offer the promise of better anti-MAC activity without the toxicity of today's multi-drug regimen.

Fungal Infections, including candida, cryptococcosis, histoplasmosis and others will become more readily treatable with the recent FDA approval of **Fluconazole**. The downside is this **Pfizer** drug's price; at \$4,000 per year for cryptococcal maintenance, this drug costs more than AZT at the new lower price and dose. Yet, because it is oral, Fluconazole offers the hope of providing effective prophylaxis against serious fungal infections, and remission of chronic candidiasis. **Janssen's** rival triazole product, **Itraconazole**, is a cheaper, but still experimental, oral antifungal, and **Schering's** new **SCH 39304** seems to be coming along fast; it's oral and non-toxic.

Other opportunistic infections, while rarer than the five major pathogens, demand intensified research. These include several already designated under the rubric of AIDS by the CDC such as **progressive multifocal leukoencephalopathy**, which has responded to crude antivirals such as **Ara-C** -- newer antivirals should be tested against PML; and **cryptosporidiosis**, which remains a devastating affliction for 5-10% of PWAs. While early results with **Diclazuril** and IV **Spiramycin** suggest potential benefits, the best dosage of the former may be higher than those yet tested, and the latter is, unfortunately, intravenously administered. There are several newly discovered pathogens whose contribution to HIV disease is still unclear, such as **microsporidia** and **mycoplasma incognitus**. The former responds to no known treatments, while the latter (if Lo's work is confirmed, and its pathogenicity documented) seems responsive to **doxycycline** and several other antibiotics.

HIV associated neoplasms are being treated with highly toxic therapies used for other cancers. Most of these cancer drugs are unpleasant and immunosuppressive; sometimes they are fatal. There are persistent suggestions that **Kaposi's sarcoma** and **non-Hodgkins lymphoma** may be linked to

¹⁰ ACTG 077P, accrual = 3, NIAID Clinical Trials at a Glance, 1.12.90.

¹¹ According to S. Nightingale at the FDA Anti-Viral Drugs Advisory Committee, 4.90.

unknown or unproven pathogens -- KS to some undiscovered organism, the lymphomas to **Epstein-Barr virus**, while **Papilloma virus** related **anogenital**, especially **cervical cancer**, appears to also be a growing problem. If these suspicions could be confirmed, and agents found, perhaps cancer prophylaxis could be implemented.

Several competing teams are working on the pathogenesis of KS. While it seems to be accelerated by HIV-associated growth factors (the lat gene may upregulate interleukin-6 -- **IL-6** -- and transforming growth factor beta -- **TGF-beta**), there may be an underlying organism responsible. HIV's ex-discoverer **Robert Gallo** claims to have a non-toxic agent which knocks out KS in vitro, but isn't telling anyone what it is, leading to suspicions that patent concerns are delaying the development of a major breakthrough against KS. Gallo's agent should be exposed and subjected immediately to clinical trials.

**"You cannot rule out the possibility that there
is a carcinogenic effect from the AIDS drugs."**

- Samuel Broder¹²

Recently detected increases in the rate of **lymphomas**,¹³ in both new AIDS cases and in long-term survivors, raise the troubling issue of whether AZT (which is known to be mutagenic in vitro, and carcinogenic in vivo to female test animals) increases the risk of lymphoma, or whether they are simply a manifestation of later-stage AIDS that AZT assists in helping people survive until. Multi-drug cancer regimens (such as CVP, CHOP, COMP, BACOP, mBACOD, COMLAX and PRO-MACE/MOPP) remain highly unpleasant.

Progress in treating HIV associated cancers has been impeded by the lack of support from the ACTG Executive Committee. The ACTG Oncology Committee is composed of some of the preeminent researchers in the field, and has the highest enrollment of its trials of any ACTG research committee. Nonetheless, in March 1990 the EC cancelled all the Oncology Committee's high priority studies, and assigned it a study the committee did not want (oral VP-16 for KS). The Oncology Committee threatened to resign en masse, and after a showdown with the EC, some of its studies were restored. This story demonstrates that, even within the scientific world, it pays to act up.

B. Pre-Clinical Considerations

Pre-clinical stages of AIDS drug development deserve more intensive scrutiny and decisive changes.

Several powerful test tube compounds have been delayed for years while sponsors scrambled to secure patents and worldwide licensing arrangements. The 2-year delay in starting the clinical trial of trichosanthen (compound Q) is just one example. From all indications, Robert Gallo is holding back from announcing an agent which might treat KS until the Japanese sponsor secures a US patent. These murderous practices, rooted in greed, must cease.

- **The US Patent Office must expedite review of all potential AIDS treatments.**
- **Researchers who delay publication or clinical trials while waiting for patent and licensing arrangements should be subject to sanctions, including removal of NIH grants.**

¹² Lawrence K. Altman, New York Times 6.12.90

¹³ Marilyn Chase, Wall Street Journal, 6.11.90; Lawrence K. Altman, New York Times, 6.12.90.

Potential anti-HIV agents are usually screened in immortalized (cancer-derived) T cell lines. These models may be of limited utility; HIV infects over 12 human cell types, and activity in the macrophages may be just as important as anti HIV activity in T cells. Furthermore, for years in the US, anti HIV drugs were screened against the HTLV-IIIb strain of HIV (the one that turned up in Gallo's Petri dish some months after the French shipped him a genetically identical LAV isolate). As one Harvard researcher recently remarked, "we don't see this strain much in the US." Hence:

- * **Lab screens for anti HIV activity should use a variety of cell lines, including T lymphocytes and monocyte/macrophage lineages, and including chronically infected as well as acutely infected cells.**
- * **Lab screens for anti HIV activity should use a variety of HIV strains, including fresh clinical isolates.**

Many months and years are wasted while drug companies replicate work already done abroad in the USA, to meet FDA requirements. With the rapid approach of European economic union in 1992 comes an opportunity for FDA to standardize procedures for acceptance of data developed in Europe.

- * **FDA must set up a process to accept pre-clinical (and clinical) data from abroad.**

Many unnecessary animal studies are done with anti HIV drugs before they enter humans. There is no good animal model for AIDS. Other mammalian lentiviruses each exhibit unique activity, and drugs may work against them, but not against HIV, and vice versa. Mutant species like the rabbit model, the SCID mouse and others may be infectable with HIV, but they do not develop AIDS. (Mice live less than 3 years, much shorter than the latency for HIV, so it is hard to tell what is the relevance of these recombinant rodents).

- * **Pre-clinical animal studies of anti HIV drugs should be restricted to searching for gross organ toxicity, and patterns of pharmacokinetics. Animal studies for carcinogenicity and teratogenicity can be conducted concurrently with phase I trials in humans.**

Many compounds show test tube anti HIV activity because researchers fail to attempt to replicate the situation inside the body. Recombinant CD4, for example, blocks virus binding to T cells in a test tube culture, but when antibodies from HIV positive persons are added, the drug is inert. This may explain CD4's lack of clinical activity.

- * **Test tube assays for HIV binding inhibitors and other agents that work on the viral or cell membranes should compare antiviral activity in the absence and presence of HIV antisera.**

With opportunistic infections, in most cases, there are good animal models for the disease (mouse CMV, cat toxoplasmosis, beige mouse MAC, etc.) In these cases, valuable suggestions of efficacy and dose response can be obtained in pre-clinical studies.

- * **When there is a good animal model for an AIDS associated pathogen, pre-clinical studies should measure the relationship between dosing levels, plasma levels and efficacy.**

The National Cancer Institute (NCI) has a massive program to screen off-the-shelf compounds in vitro for anti HIV activity. Existing compounds should be screened rationally against the various opportunistic pathogens as well.

- * NIAID's Development Therapeutics Branch (DTB) should conduct a massive screening program of off-the-shelf compounds for signs of activity against all AIDS associated pathogens, in conjunction with its National Cooperative Drug Discovery Group for Opportunistic Infections (NCDDG-OI).

C. New Drugs for the 1990s

Last year, in Montreal, ACT UP called for the immediate release of ddI, EPO, Fluconazole, Foscarnet and GM-CSF. Since then, over 10,000 people have received ddI through phase II trials and expanded access. EPO has been distributed to over 1,000 people under a treatment IND, and is said to be nearing NDA approval for its AIDS indications. Fluconazole was approved in January 1990. Foscarnet remains unavailable for most people who need it, and manufacturer Astra's promises to sponsor an expanded access program ring even more hollow than they did one year ago. While GM-CSF sponsor Schering-Plough has an ad hoc single patient exemption, GM-CSF also remains far too inaccessible to most people who need it.

There has been virtually no progress in developing seven treatments ACT UP listed as deserving faster testing -- ansamycin, CD4-exotoxin, CD4-immunoadhesin (CD4-IgG), Diclazuril, Hypericin, passive immunotherapy and peptide T. Ansamycin (rifabutin) has entered a multi-center study for prophylaxis of MAC in community-based research sites. The CD4s look less promising this year than last; NIAID nonetheless is proceeding ahead with four ambitious trials. Diclazuril has shown early signs of efficacy at high doses. Hypericin will be lucky to enter a phase I trial (in its synthetic IV form) in July. Passive immunotherapy remains mired in an unattractive dispute between biotechnology companies. Peptide T has completed a trial in Boston, and after much pressure from activists, NIAID and NIMH¹⁴, have agreed to collaborate on a phase II trial.

As activists make increasing headway with regulators, the bottleneck in AIDS drug development seems to recede towards the beginning of the process, when compounds are taken from test tube and animal studies and administered to humans for the first time.

Nonetheless, there are some therapies about which enough is known to licence them immediately on Parallel Track, or approve them. Below are some such treatments, along with recommendations for those in earlier stages of testing, which show enough promise that they should be fast-tracked.

1990: Drugs we need Now

Drug	Indication	Sponsor	Status
Azithromycin	MAC (?), toxo	Pfizer	NDA filed (non AIDS)
ddC	HIV infection	Hoffman-LaRoche	Phase II/III; limited "expanded" access
Foscarnet	CMV, ACV resistant HSV	Astra	Phase II/III
G-CSF	Neutropenia	AmGen	NDA filed
GM-CSF	Neutropenia	Schering/Sandoz	NDA filed
Itraconazole	Fungal infections	Janssen	Phase II
Trimetrexate	PCP, toxo (?)	Warner-Lambert	Phase II/III (endless ACTG); Tx IND

¹⁴ The National Institute of Mental Health -- part of the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA), not part of the NIH. NIAID has not collaborated well, thus far, with its sister institutes.

Treatments for fast-track testing - consider for Parallel Track

Clarithromycin	MAC (?), toxo (?)	Abbott	Phase I/II; approved in France
FIAC	CMV	Oclassen	Phase I (ACTG)
566C80	PCP, toxo, crypto	Burroughs	Phase I (B/W)
Oral DHPG	CMV	Syntex	Phase I (ACTG)
PATH	HIV infection	HemaCare vs	
		Medicorp	Phase I/II
Peptide T	HIV, GI disorders	Integra	Phase I/II
Rifabutin	MAC	Adria	Phase II/III
SCH 39304	Fungal infections	Schering	Phase I (ACTG)
TIBO R82150	HIV-1	Janssen	Phase I (UK)

Treatments for fast-track testing - still Pre-Clinical

BV-ara-U	HSV, VZV, EBV	Bristol-Myers	ACTG "high priority"
HPMPC	HSV, CMV	Bristol-Myers	-?-
Hypericin	HIV, HSV, CMV (?)	ViMRx	ACTG Phase I "imminent"
PMEA	HSV, CMV	Ciba-Geigy	-?-
Protease inhibitors	HIV	Abbott, Merck, Roche,	
		SKB, Upjohn	-?-

The bottleneck in AIDS treatment lies in the failure of Federally funded research programs to bring promising test tube compounds rapidly into Phase I clinical trials.

NIAID officials have told ACT UP that, while conducting more phase I studies was desirable, the ACTG might not be the proper program for carrying out this mission.¹⁵ Yet the intent of Congress, in funding the original AIDS Treatment Evaluation Unit (ATEU) program, predecessor to the ACTG, was to fund small phase I and early phase II trials. As soon as AZT came along, NIAID and its funded investigators eagerly jettisoned plans to test new drugs and took on the task of mapping out AZT's spectrum of activity.

We suggest a reversal of the ACTG's pattern, with the Federal program funding small phase I/II studies, and pharmaceutical sponsors carrying out larger efficacy trials at community based research sites around the country.

ACT UP, at its NIH demonstration on May 21, demanded that NIAID commit itself to test at least 30 new drugs a year in small phase I/II safety/activity studies. In its reply, NIAID called this proposal "arbitrary."

Below are 99 compounds which have been shown to have at least in vitro activity.

Surely at least 30 of these are worthy of NIAID's attention. In July, ACT UP will issue a more detailed report on the diverse classes of compounds emerging from in vitro work, and will work with other groups to develop a consensus about which agents must enter phase I trials this year.¹⁶

¹⁵ June 12, 1990.

¹⁶ This idea comes from John James, of AIDS Treatment News.

99 Compounds that could enter Clinical Trials in 1990-91

* denotes class of agents; - denotes specific compound

60 ANTIRETROVIRALS

- Adenallene
- Aerosolized glutathione
- 2-amino-6-fluorodeoxyuridine (FddP)
- Anti gp 120 antibodies/ high affinity binding primary neutralizing domain (PND)
- Anti interferon alpha (anti-IFN-alpha) antibodies
- * Anti-inflammatory agents
- * Antisense oligonucleotides
- Anti-tumor necrosis factor (anti-TNF) antibodies
- Arachidonic acid inhibitors
- * Aromatic polycyclic diones, including Hypericin, pseudohypericin and soybean saporins
- Aurintricarboxylic acid (ATA)
- BIRG 6587
- Carbovir
- CD4-based peptide derivatives (e.g., CD4 74-92, 81-92)
- CD4-Antibody-pokeweed mitogen conjugate (CD4-Ab-PWM)
- Cyclobut-G
- Cytallene
- * Dideoxynucleoside analogues such as ddC and FddT (FLT)
- FddCIUrd (3'-fluoro-2',3'-dideoxy-5-chlorouridine)
- Glycyrrhizin
- HEPT [1-(2-hydroxyethoxymethyl)-6-phenylthiothymine]
- Hydroxychloroquine (plaquenil)
- * Integrase inhibitors
- Interleukin-4 (IL-4)
- Iso-ddA
- Mutant rev
- Mutant tat
- NAC (n-acetylcysteine)
- Oxathiin Carboxanilide (anti-HIV-1 only)
- Oxamylaric acid
- Oxophenarsine
- PATH / passive immunotherapy
- PMEA (phosphorylmethoxyethyladenine)
- PMEDAP
- * Protease inhibitors (e.g., Roche compound XVII)
- * Ribosome inactivators (e.g., trichosanthin, mormorcharin)
- * Ribozymes
- * RRE oligonucleoside analogues
- * Novel, non-nucleoside RT inhibitors (e.g., Upjohn compounds U-80493, U-78036 + U-76081)
- Soybean saporins
- * Sulfated polysaccharides (e.g., pentosan, carageenan, fucoidan, mannan, lentinan, heparin derivatives, GE-3-S, PVAS, PAVAS)
- * Suramin analogues
- Tamoxifen
- Tat inhibitors (e.g., Hoffman-LaRoche compound TI-1000)
- THA (Tetrahydroacridine)
- * TIBO derivatives such as Janssen's R82150

9 IMMUNE BASED THERAPIES

- * Diethyldithiocarbamate (DTC) analogues
- HIVIG
- IL2/PEG
- Iscador
- Met-enkephalin
- Plasmapheresis
- Post infection vaccines
- Prosorba column
- rgp 160

20 ANTI-INFECTIVES

8 Anti-Protozoals and Anti-Mycobacterials

- * DIMP and other pentamidine metabolites
- Diclazuril
- 566C80
- * Macrolide antibiotics such as Azithromycin, Clarithromycin and Roxithromycin
- TLC-G-65 (Liposomal Gentamicin)

3 Antifungals

- Cilofungin
- Itraconazole
- SCH 39304

9 Anti-Herpesvirals

- BVaraU (bromovinyl-1-beta-D-arabinofuranosyluracil)
- BVDU (bromovinyldeoxyuridine)
- CMV Ig (IV)
- Cyclobut A
- Descidovir
- HOE 602
- HPMPA and HPMPG
- MSL 109

3 TREATMENTS FOR GASTROINTESTINAL DISORDERS

- Asacol (5-aminosalicylic acid, Mesalamine)
- Peptide T
- Sandostat

6 CANCER TREATMENTS

- Cimetidine
- Gallo's Secret Japanese anti-KS agents
- Anti interleukin-6 (anti-IL6)
- PF4 (platelet factor 4)
- Sulfonylurea
- 2-cdA (2-chlorodeoxyadenosine)

3 TREATMENTS FOR NEUROPATHY

- Colchicine
- Mexiletine
- Nimodipine

III. CHANGING THE RULES: A Challenge to Clinical Trials Methodology

We have not devoted much attention
to how we actually do these trials.

- Daniel F. Hoth, Director
Division of AIDS, NIAID¹⁷

Because there are many questions to be asked about a drug in the course of its development, and because there are many potential HIV drugs, researchers must be prepared to rigorously set priorities. Arcane studies like the interactions of AZT with probenecid or quinine cannot be justified when there is a crying need for new antiretrovirals to replace AZT. Massive Phase III trials of stop-gap first generation nucleoside analogues can no longer be justified when resources could be better used to capture data from expanded access programs and to conduct smaller, cheaper, faster phase I/II trials of new agents.

Two years ago the bottleneck in bringing new drugs to people who needed them was in the regulatory system; last year, the drugs we needed were held up in phase II/III efficacy trials. This year a large number of new drugs are undergoing pre-clinical development, and many more are stalled, awaiting human testing.

A. RECONCEIVING PHASE I TRIALS

Since Fall 1988, the FDA has provided a mechanism whereby drugs for serious conditions such as AIDS can be approved after two phases of clinical trials. Trial designers must become more creative in order to realize this potential. Phase I trials must now tell us more than they did before. The challenge is to answer the questions about safety normally asked during phase I, while capturing data that will elucidate efficacy and provide insights into practical clinical applications. Here are some suggestions:

• **Phase I trials can produce better information about useful doses.**

In order to answer all the questions that Phase I trials for new anti-HIV drugs now need to ask, they should be staged as phase IA and IB. Phase IA should identify a range of safe, active dosages which fall between the minimum active dose and the maximum tolerated dose (MTD). The maximum tolerated dose can be easily estimated by the method of Collins and Peck (NCI/FDA) who extrapolate the MTD from the dose lethal to 10% of two species of test animals. The minimum active dose can be approximated from in vitro data (and animal data if applicable) combined with early pharmacokinetics studies.

The initiation of efficacy trials should not be postponed by ritual escalation to MTD unless there is a clear suggestion that this information will be useful.

In addition, when determining dosage, phase I studies must consider the concentration of the active species at the putative site of action. For example, in the case of nucleoside analogues, the intracellular half-life of the active triphosphate metabolite, not the commonly measured plasma half-life, is the true parameter of interest.

¹⁷ FDA/NIAID Conference on AIDS Clinical Trials: A Symposium on Methodological Issues, 11.20.90, p. 1.

* **Phase I trials can produce more information about efficacy.**

Once a safe, active dosage range has been established in phase IA, phase IB studies should randomize subjects between dosages within this range. Since these trials are expected to yield efficacy data, subjects should be randomized at the earliest possible point that safety permits. In some studies, such as the NCI's first phase I trial of ddI, subjects with lower T-cells were over-represented in the groups that received lower doses. The poor outcomes of these people were probably due to having few T-cells rather than to the dose of ddI. Yet an unwarranted conclusion was made that higher doses were more effective. This may have contributed to increased incidence and degree of dose-related toxicity during subsequent testing and expanded access. Randomization could have prevented this erroneous conclusion.

It may be that the first, best chance to produce statistically significant efficacy data will come during phase I trials. This chance should not be lost.

* **Phase I studies need to concentrate on determining the lowest effective dosage.**

Currently many phase I trials merely ask "what dosages do not kill?" The lowest effective dosages for AZT, ddC and ddI are still unknown, and the toxicities of currently accepted dosages preclude long-term therapy for most people. In the case of ddC, the drug was almost abandoned after its early, disappointing studies because sponsors did not immediately test the drug at lower, safer doses.

When one considers that people with HIV usually require many medications, it is particularly important to assure that people are not put needlessly at risk by drug interactions due to unnecessarily high doses.

* **Phase I trials shouldn't disregard information relevant to managing toxicities.**

Traditional phase I trials have concentrated on determining which side effects occur and at which doses. A well-designed phase I trial may also capture information about solutions clinically relevant to the management of these toxicities. People with HIV do not always have the luxury of being able to discontinue their medication and switching to another drug.

* **Phase I trials can test combination therapies.**

Since no existing antiretroviral will halt the progression of disease indefinitely, combination anti-HIV therapy needs to be tested. Thus, it is crucial that we learn how to study combinations of drugs during phase I. It may not always be ethically or clinically feasible to study individual new drugs exhaustively before using them in combinations. For reasons of safety, it is better that adverse interactions between study drugs are found early during closely monitored trials rather than during larger post-marketing studies.

Commercial considerations routinely delay or prevent research into optimal combination regimens. Hoffman-LaRoche, for example, is developing ddC as though it would be monotherapy for HIV. Considering its impressively toxic track record, ddC should be considered mainly for alternating treatment.

After basic pharmacokinetics and safety studies new agents developed to treat Mycobacterium avium infection should be tested in combination with the drugs found to be synergistic during in vitro and animal studies -- whether or not the same pharmaceutical sponsor markets them.

- **Phase I trials can test for interaction with concomitant medications.**

Within Phase I trials of anti-retrovirals, researchers should conduct nested studies to determine possible interaction between the study drug and those antiinfective and prophylactic drugs that are in common usage. Phase I trials for antiinfectives will have to test for interaction between the study drug, other antiinfectives and commonly used anti-retrovirals. Therefore, concomitant medication, whether for conditions acute or chronic, must no longer be cause for exclusion from phase IB.

- **Phase I trials should study diverse populations.**

Given the rough bundle of opportunistic infections and malignancies that constitutes AIDS, the idea of a homogenous HIV infected population has always been an implausible fiction. Permitting diversity among a study population will not only speed trial accrual: it will yield more widely applicable results.

New antiretrovirals should be studied in people across the entire spectrum of HIV disease and in all its different populations. A drug may have very different toxicity or efficacy characteristics at earlier stages of disease. These characteristics should be known before the drug is used in large efficacy trials and on expanded access protocols. Conducting multicenter phase I trials will provide independent confirmation of results.

- **Phase I trials should build on existing data.**

The FDA has required anti-infective drugs approved for other indications to go through time-consuming phase I trials in order to receive a new indication for AIDS. For such previously studied drugs, classic phase I trials can be abridged. Doses found safe for existing indications may be used for rapid assessment of safety and efficacy. Similarly, drugs in common usage abroad for other indications should be tested for safety in modified phase I trials, and then released for expanded access until efficacy for the new indication has been proven by a controlled trial.

- **Phase I trials need to be realistic.**

People in Phase I anti-HIV trials are often expelled from studies when they develop opportunistic infections (OIs). We now realize that the current generation of antiretrovirals does not prevent people from becoming sick. People who develop OIs during phase I studies should be able to decide to remain on the study once informed of the risk of interaction between the study drug and the treatment for the OI.

- **Women must be included in Phase 1 studies from day one of clinical testing.**

It is poor science to exclude half the species because of liability concerns and concerns for a theoretical fetus. One third of the HIV infected population worldwide is female. Are drugs being developed to treat the disease or to profit from the rapidly shrinking population of affluent PWAs (who aren't female)? If it is the former, then it is absolutely necessary to include women in early human safety and toxicity testing to document at the most research intensive point in drug development any possible differences in metabolism of an agent, as well as any women --specific side effects. To exclude women from early drug testing is to test an agent incompletely and inefficiently.

B. SPEEDING UP PHASE II/III

*** Multiple questions for single trials / Multiple trials for single subjects.**

Given the urgency of the AIDS epidemic and the many questions that need answers, no researcher conducting a large efficacy trial should be content to ask a single question.

The complexity of AIDS adds considerable difficulty to the problem of designing trials which are both ethical and scientifically productive. Hitherto many drug sponsors and investigators have ignored the best interests of the patient in order to serve an implacable methodology derived from studies of other, very different diseases.

AIDS treatments cannot be studied in isolation, because people with AIDS must take many concomitant medications. Currently, trial participants often conceal their use of off-trial drugs so as not to be expelled. More rational entry criteria would incorporate diversity; and ongoing disclosure of all concomitant medications should be encouraged. Randomization will distribute the effect of concomitant treatments among the study groups, and more information about real world interactions will be gathered.

Efficacy questions can be answered simultaneously, rather than sequentially. People can and should be able to participate in more than one clinical trial if they wish. For example, patients might choose to be in a trial of an experimental anti-HIV agent while participating in one or more studies of prophylaxis for opportunistic infections.

Protocols may be designed with nested studies that investigate questions such as drug interactions or synergies. The key is to develop flexible models that offer people with HIV maximum choice, and provide the highest standards of clinical care.

*** Efficacy trials must be flexible.**

As the course of the disease changes, study questions may also change. A protocol that fails to adapt to changes in disease patterns and state-of-the-art therapeutic management will yield inadequate answers at the end of a long, expensive study. As new anti-HIV agents emerge from phase I, trials should be flexible enough to allow for the addition or removal of one of the study drugs, changes in eligibility criteria, or different endpoints.

*** Integrate the standard of care into trials / Study standards of care.**

Trials should be oriented to finding optimal treatments for diseases rather than approving drugs. Sponsors may be reluctant to conduct such trials, but these are trials that are appropriate for a government to conduct on behalf of its people. Trials sponsored by pharmaceutical companies are oriented towards drug approval; such pivotal trials are inflexible by definition. Drug marketing approval can not be the ultimate goal of all AIDS trials.

*** Design trials that people want and need.**

It is coercive to limit expanded access in order to enhance enrollment in efficacy trials. The challenge is to design trials in which people want to participate. ACTG trial 081, a multi-modal OI prophylaxis study, is a necessary, innovative trial that people were eager to join.

* **Pregnant women must be allowed to participate in all efficacy studies.**

Trials must be designed with a contingency plan to stratify women who become pregnant while on protocol and who wish to carry to term or to abort. Animal teratogenicity studies must be initiated by the time Phase I studies have begun to show a range of active doses, or by the end of Phase I, whichever is sooner. Depending on the known and potential activities/toxicities of a drug a woman may decide to withdraw from the trial during pregnancy. If a woman makes that decision, then there must be a treatment arm for her to return to after she has given birth. If a woman leaves a trial due to pregnancy, she must be allowed to receive the study drug after the trial ends as if she had completed the protocol. Women must be allowed to receive drugs that are in FDA Pregnancy category B, and if necessary C, in clinical trials.

* **Combination efficacy trials.**

Investigators have been reluctant to draw conclusions about efficacy from the few pilot combination studies conducted to date. Preliminary results from the alternating AZT/ddC trials suggest that alternating antiretroviral therapy prolongs the efficacy and lowers the toxicity of the individual agents. Yet sponsors have done nothing to follow up on the results of these small, innovative studies. ddC has recently been released on a strictly limited program as a single agent, but its optimal use will probably be in combination or alternating use. (The ACTG has a small trial of the combination of AZT and ddC, ACTG 106. More recently, a small, privately sponsored, 5-center study of the combination of AZT and ddI opened.)

Sam Broder is conducting a 14-person study that alternates doses of AZT, ddI, and ddC weekly. This study is too small to yield data about the regimen's efficacy. Although these agents have been studied individually for years, no large efficacy trial for this regimen is on the horizon. In the meantime, some people with AIDS are combining or alternating these drugs on their own.

Sponsors may be unwilling to conduct studies of combination therapies, although they may offer the most promise. Therefore, Federal research programs must mandate such trials. The US government holds the patents on ddC and ddI (Hoffman-LaRoche and Bristol-Myers hold licenses). The government can persuade sponsors to provide drugs for combination studies.

And the government should act quickly. Once ddI and ddC are licensed, researchers may have less opportunity to conduct well-controlled studies of various combination and alternation regimens. (One ACTG investigator has gone so far as to suggest that yearly cycles of different single agents may overcome resistance to any one agent.)

* **Large Simple Trials.**

As the lag in developing combination therapy demonstrates, we need new models for conducting large scale trials during or after the period when efficacy is proven. Recently, many biostatisticians have discussed the concept of "large simple trials." A large simple trial is an efficacy trial with liberal inclusion criteria that gathers a smaller amount of data than traditional efficacy trials do. This suggestion has received considerable support from researchers, the AIDS community, and individuals within the FDA. These trials could offer thousands of people potential therapy as well as gather valuable data. The parallel track program provides the opportunity to make the idea of large simple trials a reality. See "Middle Track" below.

Decision Tree Trials

Clinical trials for all serious AIDS associated conditions should be available for all people with HIV. In this decision tree model, substantial data might be gathered while people with HIV negotiated the changing choices available to them. People would be able to enter a clinical trial at any stage of disease and choose between a standard of care arm and randomization to one or more experimental treatment arms. For example, people who are asymptomatic could choose standard therapy (AZT) for HIV, then join a trial of Imuthiol as an immunomodulator. Later on, they could join prophylaxes trials, and treatment trials if opportunistic infection occurs. Flexible allocation schemes would add new arms, randomizing at an equivalent ratio whenever new experimental agents became available for efficacy trials. A good example is the foresight exercised by the designers of the SOCA protocols, who have considered adding a new anti-CMV agent (such as FIAC or oral DHPG) to their comparative trial of foscarnet and ganciclovir, as soon as they become available.

C. HOW TO IMPROVE ALL PHASES OF TRIALS

*** Adopt rational entry criteria for clinical trials for HIV-related drugs.**

Most AIDS clinical trials exclude people who do not have certain baseline values as measured by a battery of laboratory tests. Most people with AIDS "fail" at least one. Researchers have always preferred their sick people relatively well: it's easier to measure the response to the study drug. To cling to this preference for HIV trials has made a shambles of accrual efforts, and ensures that even successfully completed trials tell sadly little about how to use a drug in the real world. HIV trials require exclusion criteria tailored to people with HIV infection. The status quo is untenable: it is utter absurdity to design trials for AIDS drugs that routinely exclude most people with AIDS.

*** Include all people with HIV infection in trials.**

The underenrollment in clinical trials of special populations affected by HIV (such as intravenous drug-users and people of color) is slowing the research process. As the epidemic moves more and more into these populations, their underrepresentation becomes more and more severe. Equity demands that the research establishment redress this disparity, and so does practicality. Unless the research establishment reaches out to these populations, there is no hope of completing large efficacy trials quickly enough to benefit all people who are symptomatic today. The establishment must break with its standard clinical trials referral patterns that all but eliminate everyone but the patients of wealthy academic medical centers and their small circles of affiliated doctors.

*** Employ direct markers of virologic and immunologic activation in AIDS clinical trials**

Standardized, wide-scale use of new techniques like plasma viremia and polymerase chain reaction (PCR) may mitigate the interminable discussions about "surrogate" vs "direct" markers, and provide rapid means of confirming anti-HIV activity in phase I studies.

Much ado has been made about using surrogate markers in assessing the efficacy of anti-HIV drugs. Those markers which are useful are not surrogate, and those markers which are surrogate are not useful. The useful markers -- CD4 cell counts, percentages, p24 antibody and antigen levels and HIV plasma viremia -- are direct markers of immunologic or viral activation. They should be regarded as such. Methods of measuring them should be standardized, research labs accredited, and efficacy trials may be greatly shortened. If a new compound affects these markers (for example, causing a rapid and sustained drop in HIV plasma viremia), it could rapidly be distributed through Parallel Track, while

efficacy trials far smaller than currently conducted could assess long-term outcomes and the safety of chronic therapy.

* **The rights of trial participants to continued therapy.**

Subjects put their bodies on the line. Yet too often their access to the study drug is cut off at the end of the study period. Pharmaceutical companies should acknowledge the contribution of participants in clinical trials. People who take part in clinical trials must be guaranteed a supply of the study drug should they wish to continue taking it. The rights of people who are willing to assume the risks of early drug research must supersede the narrow financial interests of sponsors. Guaranteeing continued therapy will likely have the subsidiary benefit of improving trial accrual.

* **Participation of community members in clinical trial design.**

The communities affected by AIDS must be involved in protocol design, to ensure that the clinical trials that are conducted are necessary and practical. In addition, large efficacy trials require the collaboration of many members of the various communities affected by the disease in order to be successful. Including community members in protocol design will foster such cooperation.

* **Develop methods of testing other, non-pharmaceutical treatment modalities.**

There are treatment modalities which are systematically excluded from government, industry and university sponsored clinical trials. Some of these approaches, such as traditional Chinese medicine, have been used for thousands of years. In such cases, phase 1 trials should be abridged, incorporating known data. In some cases, there are preliminary indications of efficacy derived from treatment uses abroad; these should become the basis for systematic clinical research in the USA. Among these approaches are traditional African herbology, Chinese medicine, homeopathy, macrobiotics and other nutritional regimens, Indian Ayurvedic medicine, and vitamin and mineral-based therapies.

D. NOTES TOWARD A PEDIATRIC TREATMENT AGENDA

Minors are typically excluded from clinical trials as a matter of course. The reason most often cited is concern for the safety of the child. Experimental drugs do not have well characterized toxicity profiles. The assumption here is that toxicity data gleaned from adult trials will figure in the construction of pediatric protocols, that somehow, if we understood the drug's toxicities in adults more completely, we'd be better able to deal with toxicities in children.

The idea of letting adults assume the risks in toxicity studies, to protect children, is obviously appealing. Unfortunately, the "truths" upon which this idea is based are philosophical rather than scientific. Toxicity data yielded by phase II and III trials in adults does not have significant bearing on the way pediatric studies are designed and implemented.

Phase II/III trials survey for toxicity, rather than closely defining it. They are designed to answer extremely broad questions, characterizing the responses of populations rather than those of individuals. Such trials quantify the likelihood of various adverse reactions, but provide precious little in the way of guidance for optimizing individual therapy, or managing toxicities. The severity, duration and frequency of the reported side effects, how they were discovered, and the value of different approaches to their medical management are seldom discussed in journal articles.

Many drugs are effective at much lower doses in children than in adults. Dose/response relationships are often different for children. Since these relationships are elicited in phase I pharmacokinetic studies, this is the time and place to learn how to protect children from toxicities.

Toxicity issues impact differently on children than on adults. While adults may be willing to endure periods of drug-related discomfort if they perceive long-term benefits, children are often less willing to tolerate such discomfort.

HIV infection is briefer and more acute in children than in adults; hence valuable efficacy data can often be gathered faster in pediatric populations. Phil Pizzo's studies of AZT in children with HIV provide some of the most compelling data on AZT's antiretroviral activity and its ability to restore neurological and cognitive functions.

Simultaneous implementation of phase I pediatric and phase II adult trials will facilitate the development of unbiased pediatric results. Toxicity data are particularly vulnerable to the effects of bias. If a drug is purported to be nontoxic in adults, this could bias pediatric investigators to discount side effects reported by their subjects even more than they do now.

More children have already suffered and died due to untreated HIV infection than will ever die of drug reactions. Waiting until adult efficacy studies are completed before initiating pediatric studies endangers more children than it protects. Regulators and investigators often deal with the fact that HIV infection is lethal to children as if this issue were only peripherally relevant.

IV. PARALLEL TRACK + a Proposal for a "Middle Track"

A. Parallel track

One of the few bright spots in a depressing year for AIDS treatment research was the genesis of the Parallel Track and its development by an unprecedented cooperative effort between activists, researchers and regulators. First proposed by Jim Eigo in April 1988, and subsequently brought to public attention by Anthony Fauci in spring 1989, Parallel Track had its roots in the prolonged and agonizing DHPG approval process.

DHPG (ganciclovir), the first drug with powerful anti-CMV activity, was first synthesized by 4 rival teams in 1982. Until then, there had been no treatment effective against CMV retinitis or colitis, which led to blindness and wasting, respectively. Subsequently, a patent battle ensued between Syntex and Burroughs-Wellcome. Uncertainty over the result led Syntex to neglect to conduct well-controlled clinical trials, but the company did distribute the drug to thousands of people with CMV retinitis under an FDA approved compassionate use ("single patient") IND. In November 1987 the FDA Anti-Infective Drugs Advisory Committee, not yet sensitized to the realities of AIDS, voted not to recommend approval, in spite of the objections of its two ophthalmologists.

Compassionate use distribution continued through the end of 1988, when, in an effort to force people into a delayed treatment controlled trial, NIAID and the FDA restricted access to the drug. A widespread outcry culminated on February 1, 1989 in an ACT UP demonstration at a speech given by Ellen Cooper of the FDA. That day, 3 ACT UP members met with Fauci, who promised to intervene with FDA to restore compassionate use access. Three weeks later, the FDA relented, and in June, despite the lack of data from controlled trials, FDA approved the drug for marketing.

Throughout those months, Fauci maintained that Syntex's mistake had not been distributing the drug, but failing to conduct proper studies concurrently.

The solution, Parallel Track, was designed to provide access to a new drug with proven safety for people intolerant of standard therapy and unable to enter clinical trials of alternatives.

ACT UP spearheaded an effort to develop guidelines for Parallel Track, and these were endorsed by 20 AIDS groups and the FDA Anti-Viral Drugs Advisory Committee on August 17, 1989. The National AIDS Program Office (NAPO) then convened a task force, including members of ACT UP and Project Inform, to draw up detailed recommendations.

The Pharmaceutical Manufacturers Association, in spite of years of deregulatory fervor in Washington, was unduly worried by the implications of Parallel Track, citing tired concerns about liability and cost, and significantly delaying implementation.

After a tortuous progress through the byzantine Health & Human Services bureaucracy, the Parallel Track regulations were published as a proposed rule in the Federal Register on May 21, 1990.

Under the rule, candidate drugs for Parallel Track will be eligible after completing phase I trials, showing acceptable safety and suggestions of activity. The AIDS Research Advisory Committee (ARAC), mandated by the Health Omnibus Programs Extension (HOPE) legislation of 1988, is empowered to recommend a drug for Parallel Track. This panel, however, has not yet met, halfway through its two-year term.

Ultimately, it will be up to FDA to approve a drug for Parallel Track, but community input will be heard at the ARAC level. The proposed rule also contains guidelines for removal of a drug from Parallel Track, should the drug prove too toxic, should efficacy trials conclude the drug doesn't work, or should expanded access impede the controlled trials.

Simultaneously with the bureaucratic travails of the official Parallel Track, a prototype was being carried out with ddl. Last year in Montreal, we called for "an end to the quarantine of the AZT intolerant." We feared that the imminent efficacy trials of ddl, which would compare it to AZT, would deny the 50% of people intolerant to AZT any chance for alternative therapy. Much to our surprise, FDA, NIAID and Bristol-Myers were all receptive to the idea of expanded access to ddl for people intolerant of AZT and unable to participate in ACTG 118, the dose comparison trial of ddl.

In October 1989, ddl became available to AZT intolerant persons on a treatment IND, and to AZT failures on an open label safety study. These two protocols used existing (and often, previously, underutilized) FDA mechanisms for providing access to an unapproved drug. By June 1990 these programs had enrolled over 9,000 people with AIDS, more than any other AIDS related expanded access program. This represented a triumph for activism, and a breakthrough to reasonable behavior for researchers and regulators.

As a trial run, the ddl experience has taught much about the value, as well as the potential pitfalls, of Parallel Track.

Because the designated investigators were busy writing up their AZT results last fall, they did not focus on the ddl protocols until the studies were already written by Bristol-Myers and FDA. Changes in dose, formulation, and study designs led to delays at the individual sites, as institutional review boards (IRBs) insisted on approving all changes. Hence the expanded access studies opened before the controlled trials in many areas.

Moreover, many sites lacked staff to screen everyone on their waiting lists. Some people got tired of waiting and signed up through Parallel Track. Absurdly narrow (and in some cases anachronistic¹⁸) entry criteria led to unnecessarily slow accrual. Of the first 150 potential subjects screened at Memorial Sloan-Kettering in New York, only 3 were eligible.

At the same time, some investigators screamed that expanded access was ruining their clinical trials. Yet easily avoidable bureaucratic and methodologic errors accounted for most of the disparity. This didn't prevent some -- such as Douglas Richman of UC San Diego -- from claiming that "Parallel Track, as conceived and implemented, is a disaster."

The truth is that Parallel Track will not, itself, improve clinical trials. It will only mitigate the slowness of the research system. If it is to succeed, the controlled trials to which it is parallel must be designed to be as attractive as possible, and relevant to the real world.

Other investigators, after initially opposing Parallel Track, came to support it. These include Martin S. Hirsch of Harvard and Paul Volberding of UC San Francisco.

Criticism of the program recurred in March, however, after an ACTG investigator opposed to Parallel Track seems to have leaked the number of deaths on expanded access to a reporter. The subsequent news story spread panic among people with AIDS, and heartened the methodologists who demand that gathering data must precede access.

While the suggestions for a "Middle Track" listed below may quell the concerns of these methodologists, it is important to note that the primary intent of Parallel Track is to provide access to potential treatment for people who lack alternatives, not to gather efficacy data for a drug sponsor and the FDA.

The Parallel Track is still not a reality. Too few drugs have reached the stage where they are eligible, and too few of those are promising. The ARAC must schedule quarterly meetings, beginning this summer. And pharmaceutical sponsors must show that they are willing to participate in this new endeavor.

B. "Middle Track"

By March 1990, 290 of 8,000 people enrolled in the expanded access program for ddI had died. At the same time, less than 10 people had died in the phase II trials (N = 790, at that time). Opponents of Parallel Track used this in their ongoing campaign. Yet the two groups were not comparable: expanded access was designed for a population with more advanced AIDS; only 6 of the deaths on expanded access could be associated with ddI related pancreatitis.

Nonetheless, it has recently become clear that the doses of ddI now being studied, like those of AZT and ddC before it, are probably too high. Even the lowest doses studied in the ACTG phase I trials were active against HIV. And because some of ddI's toxicities -- such as peripheral neuropathy -- are clearly dose related, it is desirable to ascertain, as quickly as possible, the lowest effective dose of ddI.

¹⁸ ACTG 116 compares AZT and ddI in people with advanced ARC or AIDS who have never taken AZT. Because of the recent expansion of AZT's indication to people with under 500 T cells, and because many people with HIV were taking it before this expansion, the population most accessible to this trial contains few "AZT virgins." The inclusion criteria should be expanded to include people with fewer than 500 T cells.

If Parallel Track had been implemented with an optional efficacy component (here dubbed "Middle Track"), people enrolling at sites capable of collecting more detailed -- but still minimal -- efficacy data could participate in a randomized form of Parallel Track which would compare various doses of the Parallel Track drug, and generate rapid efficacy data. (For example, with ddl, if mortality were measured in expanded access, and different doses used, we might have learned a lot more about ddl's usefulness in the real world). Sites appropriate for Middle Track would include community-based clinical trial groups and qualified physicians' offices and public health clinics.

Such a Middle Track would add a minor administrative cost to a sponsor's expenses for participating in Parallel Track, but it would yield a gold mine of real world efficacy data. This trade off seems potentially valuable, as long as the Parallel Track were still available through clinics and doctors who could not afford the extra data collection activities.

In other words, Middle Track would, like Parallel Track, be primarily a distribution program, with a secondary goal of gathering minimal efficacy data. The endpoints could be similar to those used in large simple trials.

V. ACTIVIST MANDATES

A. To President Bush and the US Congress.

This year AIDS research funding isn't even keeping up with inflation - it's due to rise about 7%; the AIDS caseload will double, to 200,000. Double the entire NIH biomedical research budget. Restore funding for 50% of grants deemed worthy of funding, as occurred in the 1970s. Stop pitting people with different diseases against each other. Involve people with different diseases in research on those diseases. Speed up patent review of new treatments. Extend Medicaid coverage to all Americans lacking health insurance. Mandate states to cover AIDS therapies, including off-label uses. Mandate insurance companies to cover off-label uses of approved therapies, and to contribute towards medical costs associated with participation in clinical trials. Guarantee health care to all Americans. Remove INS restrictions on the travel of HIV infected persons in and out of the USA. Stop HIV testing for immigrants. Provide leadership and insist on accountability and rapid progress against AIDS and all other serious and fatal diseases. Fund and implement the 1989 PHS guidelines on monitoring and early intervention for HIV infection, including free periodic T cell testing, early antiretroviral therapy and PCP prophylaxis. Get the FDA some computers and a new campus. Raise NIH salaries to make them competitive with those of industry. Demand a conflict-of-interest policy mandating full disclosure of all ties with industry for investigators receiving government funds.

B. Blueprint for a More Productive A.C.T.G.

On May 21, ACT UP stormed the NIH to demand a more efficient, humane research enterprise. Most of those involved in AIDS research, whether at NIH or in the academic sites funded by the ACTG, are talented and dedicated professionals. Yet the structure of the ACTG system denies them the chance to work to their full abilities, and, in its first five years, the ACTG has been a dismal failure.

Next year, the second five-year round of ACTG grants will be awarded. In the first five years, the landscape of AIDS has been utterly transformed by treatment advances, most of them developed outside the ACTG. Yet the \$100 million annually awarded to this program can be used better, and should not be scrapped. In its next phase, the ACTG has the opportunity to learn from its mistakes, incorporating new developments in treatment and in clinical trial design, and to open the process to people with AIDS and activists at every level.

In discussions with investigators over the past months, it has become clear that many talented researchers are not satisfied with the system, and do most of their constructive work outside of it. This is because ACTG research priorities are set in private by a small number of principal investigators who sit on the Executive and Primary Infection Committees, in conjunction with NIAID's Division of AIDS. Hence the emphasis on nucleoside analogue antiretrovirals, tested to the exclusion of many other approaches. The original ATEU system was divided into part A (HIV research) and part B (opportunistic infections and cancers). Some have suggested that the ACTG be decentralized, that it continue conducting multicenter trials of anti-HIV drugs, and that individual sites compete for a new form of the old part B contracts, so that investigators can pursue their interests with the guarantee that they will be able to implement their proposed studies. In other words, the present cooperative agreement system would continue for large phase II/III trials, while targeted research contracts would be issued for the major opportunistic infections and cancers, and for small phase I/II studies.

There is a precedent for this decentralized approach in the SOCA (Study of the Ocular Complications of AIDS) program, which will use ACTG sites and others to compare DHPG vs Foscarnet in treating CMV

retinitis. The design is flexible, to allow incorporation of new anti-CMV therapies as they become available. Expert ophthalmologists and trial designers are collaborating with people from the AIDS community on this project.

It is not clear at this point whether the best approach to structuring AIDS treatment research would lie in more decentralization, with targeted contracts to ensure that all major areas were addressed, or simply in a restructuring of the ACTG in its second five years. Should the program continue in something like its present form, we recommend the following changes:

Changes in the ACTG structure. The ACTG is controlled by its Executive Committee (EC), acting in concert with NIAID's Division of AIDS. The EC selects the chairs of each research committee¹⁹, and the chair in turn selects the core research committee members, who make all important decisions in private, as does the EC. Hence the program is directed from the top down. Investigator-initiated concept sheets are filtered up through the appropriate research committee, but the EC makes all final decisions. This leads to frustration for investigators whose trials are never approved, or, once approved, subsequently placed on hold. The Opportunistic Infections (OI) Committee, for example, has Pathogen Study Groups (PSGs) for each major OI. These PSGs have had studies designed and ready to go for several years, but most are never implemented.

The entire research committee should select its core committee, which should select its chair. In addition, the core committees should elect delegates to the Executive Committee, and each committee should be represented equally there. People with AIDS and activists should have full voting powers on all core committees and on the Executive Committee. Meetings should be conducted openly, with executive sessions only when a drug sponsor is presenting preliminary data.

Changes in the ACTG's research priorities. Now, virtually any complaint about the ACTG system is rebuffed with a pious invocation of the "priority setting process." This is a process to which few have entree, and even fewer influence.

The ACTG should set its priorities in an open fashion, after a debate of its entire membership, including input from people with AIDS and activists. Resources should be divided among each research committee in proportion to how much of the overall AIDS problem lies in that committee's bailiwick. Thus, perhaps half of adult trials and half of pediatric trials could focus on primary (HIV) infection. The other half could be divided between the opportunistic infections and cancers, neurology and other complications. Within both areas, a significant proportion of the research effort should focus on phase I trials of new compounds. In addition, there is no reason not to consider innovative studies designed to enhance trial accrual and compliance, and quality of life.²⁰

Currently, many drug companies have become reluctant to submit new agents to the ACTG. The February meeting of its drug selection committee²¹ was cancelled for lack of submissions. If sponsors are unwilling to use the system, the ACTG will continue to founder. If sponsors are to be brought in,

¹⁹ The ACTG has 8 research committees -- Data Management, Neurology, Oncology, Opportunistic Infections, Patient Care, Pediatrics, Pharmacology, Primary Infection -- and two resource committees, Immunology and Virology. The Immunology Committee has a working group devoted to immune-based therapies, replacing the Biological Response Modifiers Committee, which bowed out in 1989.

²⁰ The Patient Care Committee proposed ACTG 126, "Impediments to Accrual of IV Drug Users in ACTG Trials," but this initiative was cancelled by the EC in March.

²¹ The AIDS Clinical Drug Development Committee (ACDDC), technically an independent advisory body reporting to Fauci, but loaded with Division of AIDS staff, Executive and Primary Infection Committee members.

the ACTG must provide a means of guaranteeing rapid accrual into its studies, timely completion, and efficient analysis and publication of results.

When NIAID interrupted ACTGs 016 and 019, it distributed a "Letter to Physicians" around the country. Many doctors, however, are reluctant to practice medicine by press release. Alternatives to waiting for peer reviewed publication in medical journals must be developed, to speed the transfer of trial results into everyday clinical practice around the country. NIAID should consider a quarterly newsletter of research results, and must establish an Office of Patient Care to oversee the translation of data into guidelines for clinical practice.

The ACTG should also establish a committee to deal specifically with HIV disease as it manifests itself in women. Women can no longer be considered solely under the rubric of the Pediatric Committee, as they are now. Such a program would incorporate the existing Obstetrics & Gynecology Working Group, and would provide primary care to all participants who would otherwise be ineligible for lack of health care.

Changes In ACTU sites. Funding for each AIDS Clinical Trials Unit (ACTU) must be tied to performance. Sites which consistently lag should be cut off, and new sites established in areas with high HIV incidence and competent researchers. There are other impediments to accrual, however, which only the central program can resolve. The present system prioritizes trials, rewarding those who enroll large numbers in high priorities, and penalizing those who focus too much on low priority studies. All implemented protocols should be considered high priority. In addition, many trials have foundered because of poor design, or irrelevance to the needs of people with AIDS.

To mitigate all these problems, each ACTU should establish a community advisory panel to provide input on the relevance of studies, improvements in trial design, and advice on conducting outreach to the diverse affected communities.

In addition, the ACTUs need to improve communication within hospital sites. Today, many eligible participants are never screened because emergency room staff (for example) don't know about trials going on upstairs. ACTUs must have a plan to coordinate information with nearby health care institutions to enhance enrollment, and within their own institutions.

The ACTUs must enhance services to potential and real participants. Many people need transportation subsidies, and some need child care if they are to participate in an ACTG trial. These must be provided. Too often, participants are now abandoned once the trial is over. A more humane model would provide continuing HIV care for all those who have offered their bodies for science. This might enable more rapid enrollment of follow-up trials.

Those who care for participants and manage the data -- largely unrecognized, underpaid and female -- have insights into research which should be taken into account by those designing trials, and those who take the credit. State-of-the-art standards of care for people with HIV, in and out of trials, must be observed at all ACTUs.

*

C. Suggestions for AIDS Activists

- **Get Involved In your local ACTU (AIDS Clinical Trial Unit).** All ACTUs need to have community advisory panels. A community advisory panel can help set research priorities, evaluate protocols, and make sure that the all affected communities are represented in clinical trials. Your ACTU may not willingly receive your input, but you must demand to be heard. Trials done without community input and support are likely to be outdated and irrelevant, or poorly designed. If your community does not have an ACTU advisory panel, you must fight for one.
- **Get Involved In your local Community-based research organization.** Community based research organizations need the same input that ACTUs do. If your community does not have a community based research organization, think about starting one.
- **Adopt a Principal Investigator.** It is essential that AIDS activists become experts at the research going on in their communities. Meet the PIs conducting trials. Read their papers. Read their protocols. Discuss their research with them and their staff. Their staff is often more candid. Find out what they researched before AIDS. Learn their consultancy arrangements. Any scientist is influenced by received dogma and industry alliances. Challenge them to make sure that these things are not biasing their research.
- **Have a teach-in In your community.** Knowledge is our key to fighting the HIV epidemic and the HIV bureaucracy. Scientists often discount activist input, claiming we lack their experience and expertise. This is not true. Activists have made themselves experts. We must share this expertise.
- **Adopt a drug.** Many drugs seem to get lost or waylaid between discovery and approval. Studies are indefinitely delayed and people with HIV are denied access to drugs. We must be vigilant to prevent this from happening. Identify a drug you think is languishing and contact the company that produces it and the FDA officer who monitors its approval process. Find out sources of delay and seek to overcome them through letter-writing, phone calls, or direct action. Other activists from around the country are monitoring the same drugs; find out who they are and join forces for a national effort to assure speedy approval and distribution.
- **Communicate what you learn.** Share any knowledge that you gain with other activists and the public. Translate what you learn into language that is appropriate for the evening news. Hold events and demonstrations that allow you to communicate what you have learned through the media.
- **Reading is fundamental.** Get ahold of the latest scientific journals. Start a science club to discuss important articles and share what you learn. Attend scientific meetings in your community and represent your point of view.

This document is a collaborative project of the Treatment + Data Committee of ACT UP/New York. Contributors include Matthew Burns, Jim Eigo, Ken Fornataro, Garance Franke-Ruta, Mark Harrington, Bob Huff, Cassandra Freedom-Jones and Rich Lynn.
