A NATIONAL AIDS TREATMENT RESEARCH AGENDA

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ACT UP

AIDS Coalition to Unleash Power / New York

ACT UP is a diverse, non-partisan group of individuals united in anger and committed to direct action to end the AIDS crisis. We protest and demonstrate; we meet with government and public health officials; we research and distribute the latest medical information.
WE ARE NOT SILENT.

ACT UP 496-A Hudson St. Suite G4 New York, NY 10014
212-989-1114

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INTRODUCTION

The US is the epicenter of the worldwide AIDS pandemic. It has the resources – human, technological and financial – to rapidly develop drugs to prevent or treat most AIDS-related conditions. It has a global responsibility to do so. The US has failed to carry out its global responsibility. The managers of the AIDS research effort are motivated by profits, patents and prestige, not by a vision which demands solutions to the real-world problems engendered by AIDS.

Over the last year, dimly, like echoes from a distant battlefield, the voices of people living with AIDS or HIV, and their advocates have begun to reach the ears of researchers and regulators in the Federal AIDS establishment, who have finally begun to notice that something is wrong.

The crisis engendered by the dysfunctional drug development status quo may well cause consternation and conflict among US scientists and regulators. Its grimmest consequences, however, are played out every day in hospitals and clinics and, increasingly, in streets all over the world. The toll of unnecessary sickness and early death caused by HIV-related conditions mounts relentlessly while people worsen from lack of access to existing drugs of known safety and very strong indications of efficacy.

It is time to develop a comprehensive strategy to address all clinical manifestations of HIV. The US AIDS Program does not have such a strategy. We have no time to wait for them to develop one. People living with AIDS, HIV and their advocates know what must be done. The following is a set of guidelines for a sweeping revision of US AIDS research and regulatory priorities. We call upon all people working in the struggle against AIDS to put these guidelines to work.

I. 12 PRINCIPLES FOR A NEW AIDS DRUG TESTING SYSTEM

Studies are constantly announced and undertaken by people who have only the vaguest notions of how we live.

- Larry Kramer
"Where Are We Now?"
October 1982

Trials serve a dual role: researchers and sponsors want data which may lead to marketing approval; subjects want health care. Therapy is the only reason potential subjects should enroll in a trial. We will not participate in a trial unless it provides treatment for the condition being researched. No trials now underway will succeed, nor should future trials be designed, without meeting the following prerequisites:

1. **People with AIDS, HIV, and their advocates must participate in designing and executing drug trials.**

The AIDS community must be an equal partner with sponsors, researchers and the Federal AIDS Program in setting priorities for AIDS treatment research, selecting drugs to be tested, and designing and implementing protocols. We must have full voting members of every decision-making body involved in the AIDS Program, including:

* NIAID's AIDS Clinical Trials Group (ACTG) Executive Committee,
* NIAID's AIDS Clinical Drug Development Committee (ACDDC),
* FDA advisory committees concerned with AIDS treatments,
* Institutional Review Boards (IRBs) at all sites conducting AIDS and HIV-related clinical trials,
* The National Committee to Review Current Procedures for Approval of New Drugs for Cancer & AIDS (the Lasagna Committee), and
* The Parallel Track Advisory Committee.

2. **A comprehensive, coordinated, compassionate drug development strategy must ensure that all promising agents are evaluated thoroughly and, if found effective, distributed rapidly.**

The AIDS Program has no master strategy. NIH continues to rely on investigator-initiated research, delaying even the best proposals in a bureaucratic labyrinth. This passive approach produces treatment advances in bits and pieces. An overall research strategy should be coordinated with the AIDS community to develop a comprehensive plan to treat the serious infections and conditions associated with AIDS.

3. **Resources must be focused on drugs which treat or prevent opportunistic infections, not just on antiretroviral drugs.**

Most Federal research dollars fund expensive, highly toxic antiretroviral trials while people with symptomatic HIV are dying of opportunistic infections that receive little attention. No current approved treatment exists for most HIV-related OIs, including CMV, MAI, HIV wasting syndrome, cryptosporidiosis, and HIV encephalopathy.

Treating or curing the major opportunistic infections must immediately become a priority equal to finding anti-HIV agents.

4. **End the exclusion of women, poor people, people in rural areas, people of color, drug users, prisoners, hemophiliacs and children from experimental treatments. Expand staff and facilities in areas with high concentrations of HIV-infected people so trials can take place there.**

Trials should allow the participation of all infected groups. Most people living with HIV lack access to new treatments which could save their lives. Resulting data describes the new drug results only in selected, homogeneous groups, not in the overall HIV-infected population.

Children with AIDS still cannot obtain AZT outside of trials, more than 2 years after it was approved for adults.

Federally-sponsored drug trials should fund primary care physicians in areas where enrollment is impeded when principal investigators do not enroll patients who lack primary care physicians.

5. **End the exclusion of AZT intolerant individuals from trials for infections or other antivirals.**

50% of people with AIDS are intolerant of AZT. They are effectively quarantined from most antiretroviral trials, which either still test AZT or compare it with newer antiretrovirals. Randomized, comparative trials bar people intolerant of AZT from access to the very drugs which offer them the best hope for treatment.

Randomized comparative trials using AZT should have a non-randomized arm for the AZT intolerant. Trials for anti-infective drugs should allow people to enroll regardless of their AZT tolerance. Trials that compare a new to a standard treatment should include an non-randomized, open-label arm for people intolerant to the standard treatment. For example, Foscarnet trials should include people intolerant of DHPG, not exclude them like some do now.

The Parallel Track initiative for expanded, nationwide access to certain promising AIDS drugs outside of controlled clinical trials offers the first real chance to end the exclusion of the AZT-intolerant from trials.

6. Protocols should be flexible enough to accommodate new knowledge about HIV infection, allowing subjects to receive state-of-the-art care for opportunistic infections (OIs) as such standards evolve.

The major confounding factor in most clinical trials is variations in patient care. PCP prophylaxis became standard-of-care in private practice while AIDS Program trials still denied subjects prophylaxis. Up-to-date AIDS care should become standard if trials are to yield valid, replicable, real-world data. Protocols should allow subjects to use new state-of-the-art HIV and OI treatments.

7. Trials must be designed for the real world: prophylaxis permitted, placebos avoided, efficacy criteria and endpoints humane.

Prophylaxis for OIs must be permitted to all trial subjects. Scientific requirements for valid data should be balanced with human requirements for active, aggressive treatment.

Placebo trials in AIDS are a medically-sanctioned form of Russian roulette. Placebo-controlled trials do not yield quick, clean data. Participants take drugs off trial, obscuring results. Target enrollment is frequently expanded to minimize data contamination from those who drop out or take concurrent medication. Trials are prolonged, results delayed, and more people exposed to risk.

No potential trial subject with even a vestigial instinct for self-preservation will join a placebo-controlled trial. If a standard treatment exists, new treatments can be compared to that. If no approved treatment exists, new treatments can be tested against each other.

Efficacy criteria should be reasonable. FDA has delayed release of blood-boosting drugs like EPO and GM-CSF, insisting that they show direct clinical effects when, in many cases, those drugs merely bring blood counts up to levels where it is safe to use other treatments.

p24 antigen positivity should not be used as a strict inclusion criterion. Some of the AIDS Program's newer trials require a positive p24 antigen test for inclusion. Most clinicians agree that p24 is an imperfect surrogate marker of viral activity. Not all people with AIDS are p24 positive, and some p24 positive people have no symptoms whatsoever.

Endpoints well short of death should be established. Death or progression of infection are unacceptable endpoints for trials when any treatment at all exists outside of trials.

8. Clinical costs associated with trials and not paid for by sponsors should be funded by third party payors to insure that personal income is not a de facto exclusion criterion.

HCFA (the Health Care Finance Administration), the insurance companies, NIH and drug sponsors must agree on a formula to cover clinical costs associated with administration of investigational substances: hospitalization for catheter insertion, lab costs, etc., so people of all economic strata can participate in drug trials. Third-party reimbursement must include, but not be limited to, treatment IND and compassionate use protocols. All society benefits from drug development. Trial subjects contribute their bodies for research. They should not have to pay for access to investigational substances.

9. The Orphan Drug Act should be reformed so that products developed at public expense are priced fairly. In return for its multi-million dollar investment in AIDS research, the government is entitled to demand low-cost drugs for AIDS. This will make treatments accessible to people who can't afford AIDS drugs in both the US and worldwide.

Few remember that the drug law reforms of 1962 originated in Senate hearings over inflated new drug prices. The outrageous price of AZT was one of the reasons ACT UP formed in 1987. Several pharmaceutical companies are exploiting the AIDS crisis and the Orphan Drug Act to jack new drug prices up to unprecedented heights.

Most research costs for new drugs for AIDS are paid for with tax revenues. 3/4 of all people in the ACTG system are still in AZT trials. AZT research is massively subsidized by the public while huge profits are privatized in the hands of Burroughs-Wellcome. If AZT is approved for high-dose use in asymptomatic HIV-infected persons, the company will make billions. This makes a mockery of the intent behind the Orphan Drug Act.

In the case of erythropoietin (EPO), orphan drug status actually impeded release of the drug, as companies fought for pieces of the lucrative market.

Orphan Drug status is really a taxpayer subsidy for pharmaceutical research. The public is entitled to a fair return on its investment in the form of a reasonable price. Companies should substantiate their prices for orphan drugs and open their books. Drugs developed at public expense should be licensed to competing sponsors to keep prices down. Orphan Drug status should be revocable if a drug (e.g., AZT, EPO) becomes unexpectedly lucrative. If a sponsor drops a promising drug, compulsory licensing procedures should be available, as they are in Canada.

10. The community-based clinical trials network, NIH, FDA and other drug development agencies require increased staff, funding and facilities to wage a successful effort against AIDS.

At a fraction of the cost of AIDS Program trials, New York's Community Research Initiative (CRI) and San Francisco's County Community Consortium (CCC) have already provided the data necessary for aerosol pentamidine to receive treatment IND status and a recommendation for full approval. Three years and half a billion dollars later, the Federal AIDS Program has yet to produce a single drug for wide use. If a cure for AIDS were discovered tomorrow, the AIDS Program would not be able to test it for over a year. NIAID has not run its multicenter efficiently or set up good, quick trials. Staff and funding increases are necessary, but not sufficient, to improve its performance.

Because there is no overall AIDS treatment development strategy, the US has no grasp of the overall logistical needs for conducting widespread clinical trials. A comprehensive response to AIDS would include more doctors, nurses and lab technicians in Health Manpower Shortage Areas, particularly researchers, clinicians and nurses of color.

The US has the ability to expand funding in all areas of health care. What has hitherto been lacking is the political will to do so.

11. Establish an accurate, up-to-date, accessible, international registry of clinical trials and promising experimental treatments for HIV and for AIDS-related opportunistic infections.

Drug sponsors are hoarding information on life-saving treatments during an international pandemic. This is unconscionable. All trials, both Federally-sponsored and pharmaceutical, should be listed in a nationwide database when they begin. The Public Health Service (PHS) agencies should cooperate with groups like New York's AIDS Treatment Registry (ATR) to demand information from pharmaceutical companies and make up-to-date information available to everyone. PHS officials should support legislation making all clinical trial information available to the public.

FDA and NIH should help to establish international standards for exchange of drug trial data, creating international standards which could speed the availability of foreign-tested drugs to Americans and vice versa.

12. Promising new treatments for HIV and AIDS-related infections should be made accessible to anyone without regard to personal income.

FDA should become a proactive agency which protects Americans from deadly diseases, not just from unproven treatments.

The treatment IND has failed to widen access to promising experimental treatments. FDA should reform or replace its failed program to allow distribution of promising experimental substances to all who need them before full marketing approval.

A new distribution network for promising experimental treatments is needed. It should provide both primary health care and access to safe investigational substances believed effective. Data forms should be simple (like those of San Francisco's County Community Consortium) so participating physicians aren't swamped with paperwork. The FDA should immediately acquire on-line computer systems to evaluate trial data.

Companies have no financial incentive to apply for treatment IND. Few have. The Health Care Financing Administration (HCFA), which funds Medicare, refuses to acknowledge the therapeutic intent of the program embodied in its name. Following its cost-ineffective lead, other third-party payors refuse to pay for these promising drugs. People with money can pay for access to life-saving treatments, while people without money suffer more and die faster.

Most people with AIDS lack access to information about treatment IND and compassionate use drugs. Most doctors are ignorant of them. Most inner-city and rural hospitals lack staff and funds for clinical procedures associated with such drugs, even when the drug itself is provided free. Physicians lack time or staff to complete the rigorous paperwork.

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At the end of the first decade of the AIDS pandemic, we have a historic opportunity. For the first time, there is an array of promising substances ready for human testing. They should be widely distributed in treatment protocols to treat AIDS-related infections and directly combat HIV. If clinical trials continue to be badly-designed, the increasing AIDS caseload will overwhelm our society. If the Federal AIDS Program and the pharmaceutical industry work with the AIDS community to create a humane research system, patients and science will both benefit.

II. NEW MODELS FOR CLINICAL TRIALS

We need to consider alternative study designs that offer the patient maximum hope for cure and the opportunity for some control over his or her destiny. ... What I am suggesting is the need for a reexamination of all the assumptions on which the scientific requirements of the present system are based.

- Jere T. Goyan, Ph.D.
Ex-FDA Commissioner
UCSF Pharmacology School Dean
"Drug Regulation: Quo Vadis?" 1988

There is an urgent need for new AIDS clinical trial designs. Only about 7,000 Americans, less than 0.5% of the HIV-infected US population, have enrolled in an AIDS clinical trial. Accrual is impeded by poor trial design, inaccessibility, denial of opportunistic infection prophylaxis, reluctance to enroll in placebo-controlled studies and ineffective outreach to the affected communities.

A consensus is developing among the medical establishment and the AIDS community. We need better trials carried out in new, community-based institutions. Computer monitoring of serologic and clinical results can be used to evaluate optimal dosages and combinations of drugs for HIV-related conditions. New models for clinical trials will synthesize scientific and therapeutic aims.

Pharmacokinetics. A clearer pre-clinical understanding of in vitro therapeutic, toxicology and animal models will help shorten Phase I safety or pilot efficacy trials. Inadequate studies of how treatments are absorbed, metabolized and excreted (pharmacokinetic studies) often ruin efficacy trials. Examples include oral dextran sulfate and IV Imreg-1 and Ampligen. Pharmaceuticals and biotechnology companies must learn the right order in which to test substances with promising in vitro activity. Before Phase II begins, sponsors should know:

- **An assay to detect absorption in the bloodstream,**
- **Absorption, serum half-life and excretion characteristics.**

Why is there still no satisfactory serum assay for dextran sulfate absorption?

Drug delivery. The serum half-life, optimal frequency and mode of administration are major determinants of a new treatment's usefulness in the real world. If a drug (e.g., first-generation CD4), requires lifelong hourly injections, it's not a viable treatment. Availability and absorption of a drug through oral, subcutaneous (SC), intravenous (IV), intranasal, rectal or aerosolized routes should be determined at the start. Drugs with high systemic toxicity should be delivered to the site at risk. In some cases (e.g., EPO), subcutaneous injection may have a longer half-life, hence greater efficacy, than IV injection. If so, doses should be concentrated to ensure that IV injection is not required.

A suggestion for Phase I trials. It takes far too long to obtain basic safety data on a drug—a minimum of 2 years between discovery of test tube activity and the start of efficacy trials (AZT was the sole exception).

Two ways to obtain safety data faster:

1. When a drug has been used in another country at a comparable dosage, there is no need for protracted dose-escalation studies. Quick, incisive pharmacokinetics at the dose common abroad (or half that, to be cautious) is all that's required.

2. Phase II trials can begin while Phase I trials continue. It is not necessary to determine high-dose toxicity if a lower dose already found safe is sufficient to test for efficacy.

Pilot efficacy trials. Compared to antiretrovirals, efficacy in anti-infective drugs is easy to demonstrate. So placebo-controlled trials of anti-infectives are unnecessary. Measuring efficacy of a prophylaxis is easy: subjects either develop the OI or they don't. Measuring efficacy of a treatment is also easy: the condition regresses, stabilizes, or continues to advance. Comparative efficacy trials are useful with anti-infective drugs because they can compare, in a controlled setting, treatments widely used outside of trials.

Community-based trial groups could easily set up a series of quick, open-label efficacy trials of the most common OI treatments, comparing them with newer therapies. These pilot, open-label trials will provide useful information on which regimens are most effective and well tolerated.

Multicenter open-label trials. When pilot efficacy trials are promising, they should be refined and implemented at multicenter community-based sites, at the ACTUs and at other places with HIV-infected people.

Treatment protocols. Once a safe new treatment shows some efficacy, the sponsor should open a large treatment protocol (using a reformed treatment IND program or a new process) to everyone who need the new therapy, including people resistant to standard treatment. People whose reactions to standard treatment are not known can enroll in randomized, comparative trials of new vs. standard treatment. If they develop adverse reactions to the active control, they can be switched to open-label treatment with the new drug.

Post-marketing surveillance. After new drugs for AIDS are developed and marketed quickly, extensive post-marketing surveillance is necessary to refine the best dose, route and frequency. Data should also be gathered on rare adverse effects and overall survival rates. Post-marketing studies should provide treatments to subjects at no cost.

III. THE PARALLEL TRACK

[Note: the following is the consensus statement of 15 AIDS research, service and advocacy organizations presented to the FDA Anti-Infective Drugs Advisory Committee on August 17, 1989, and ratified by that committee in its recommendations to FDA and to Assistant Secretary of Health James Mason.]

The concept of Parallel Track permits the treatment use of experimental drugs while controlled efficacy trials are ongoing, thus offering earlier access to promising new treatments to people with AIDS and HIV-related conditions. This concept has been widely hailed. The AIDS community is eager to work with FDA, NIH, pharmaceutical sponsors and researchers to rapidly define and implement the Parallel Track.

Parallel Track offers the best hope to address some of the most urgent problems posed by the AIDS epidemic: the rapidly expanding caseload, the proliferation of new promising treatments, the inability of traditional research institutions to test each promising therapy, the inability of most HIV-infected Americans to enroll in controlled clinical trials, and the use by many patients, out of necessity or choice, of other medications.

The importance of Parallel Track lies in its potential to offer the widest possible access to new drugs for people who lack other-than-experimental treatment options, and to make it possible, at the same time, to proceed efficiently with drug licensing.
Existing mechanisms to widen availability of new treatments outside of controlled trials, such as Treatment IND and Compassionate Use IND, have met only a fraction of existing needs. Parallel Track may resolve access needs, provided, we believe, the principles outlined below guide the implementation of the Parallel Track concept.

1. Access

Parallel Track should encompass post-Phase I open-label treatment protocols for people unable to participate in controlled clinical trials for AIDS and HIV-related treatments. Drugs should be eligible for Parallel Track as soon as a tolerably safe dose range has been defined and preliminary evidence of efficacy has been obtained.

Drugs qualifying for Parallel Track should be accessible nationwide to qualified physicians in private practice, community hospitals, community-based health institutions, and public health clinics in addition to academic clinical research institutions.

Adverse reaction data should be gathered on all Parallel Track subjects. Whenever possible, efficacy data should be gathered as well, through organizations such as community-based research groups. The resulting

data on interactions between the Parallel Track drug and concomitant medications forbidden in controlled trials would provide valuable real world information at the earliest possible time.

2. Eligibility

Patients' eligibility for treatment under Parallel Track should be determined by qualified physicians on a case-by-case basis. However, the same access criteria should apply under different circumstances. The following groups of HIV-infected individuals should have access to treatment under Parallel Track:

* People with a condition for which there is no standard treatment.
* People who cannot tolerate the standard treatment for their condition.
* People who are failing on standard treatment.
* People who must stay on concomitant medications forbidden, but not expressly contraindicated, in trials of new experimental treatments.
* People who are too far from the site of an appropriate controlled trial.
* People who are too sick to participate in the controlled trial.

Because of the generally large number of people with AIDS and HIV disease, and because most of them will be unable to participate in controlled clinical trials, it is anticipated that the existence of Parallel Track will not compete with, but rather complement, more formal studies.

3. Oversight

Decisions regarding the definition and implementation of Parallel Track shoiuld be made by a **Parallel Track Advisory Committee**, an independent body including representatives from the Food & Drug Administration (FDA) and National Institutes of Health (NIH), but empowered with full decision-making autonomy. This committee should also have representation from top research scientists as well as the Health Care Financing Administration (HCFA), to assist it in advising on issues of third-party reimbursement for ancillary costs associated with Parallel Track drugs, including costs of administration and adverse reaction monitoring.

The Advisory Committee would also contain representatives from the Pharmaceutical Manufacturers Association (PMH) and an ad hoc position for the sponsor of the drug in question, and top research scientists.

Most importantly, the Parallel Track Advisory Panel must include full, voting representation by AIDS primary care physicians, representatives of community-based research groups, and people with AIDS, HIV and their advocates. It is the lack of such decision-making representation that has impeded all previous efforts at widening access to new AIDS therapies. If this participation is once again limited, the program may well generate the same disappointing results as Treatment IND and Compassionate Use.

As one of its first tasks, the Parallel Track Advisory Committee should consider mechanisms for assuring that any person with HIV infection who has a demonsstrable medical need for a Parallel Track treatment could obtain access regardless of economic circumstances.

IV. AIDS CLINICAL RESEARCH PRIORITIES

6 Drugs We Need Now

DDI
EPO
Fluconazole
Foscarnet
GM-CSF
DDC

8 Treatments We Want Tested Faster

Ansamycin
CD4-Exotoxin
CD4-Immunoadhesin
DDC
Diclazuril
Hypericin
Passive Immunotherapy
Peptide T

Guidelines for Research

Antiretrovirals
Prophylaxis for OIs
Treatment for OIs
Blood Conditions
Wasting & GI Conditions
Neurological Conditions
Immunomodulators
Malignancies
Addiction Treatments
Complementary Treatments

6 DRUGS WE NEED NOW

Enough is known about the following 5 treatments to release them in broadly-inclusive treatment protocols now. Such a program (which could be under the auspices of the Parallel Track) should include:

* Nationwide information distribution about the treatment,
* A central 800 phone number to access the treatment,
* Full reimbursement of clinical costs associated with its administration by all third-party payors,
* Simple data-collection forms to facilitate collection of relevant information.

DDI (DIDEOXYINOSINE). In the test tube, ddI is slightly less active than AZT, but many times less toxic. Phase I trials showed toxic pancreatitis and peripheral neuropathy at high doses, but these are reversible, and may not occur at the lower doses projected for the Phase II trials. DDI crosses the blood-brain barrier, essential for suppressing HIV in the brain. It languished for a year in endless Phase I dose-escalation studies. When Phase I trials show safety, Phase II trials should be allowed to begin while small Phase I studies for the maximum tolerated dose continue. In such cases, the toxic dose is probably much more than the necessary effective dose anyway.

DDI could be a good treatment for:

* People who cannot tolerate AZT at all,
* People who become anemic on AZT and need transfusions,
* People with CMV retinitis who need to take DHPG, which usually cannot be taken with AZT because both suppress bone marrow,
* People who have low white blood cell counts from AZT, DHPG or pyrimethamine, a common treatment for toxoplasmosis.

EPO (ERYTHROPOIETIN). EPO, a genetically engineered version of a naturally-occurring human enzyme, causes proliferation of red blood cells in people with AZT or HIV-related anemia, kidney disease or cancer. It can raise people's hemoglobin counts and reduces their need for transfusions. Its approval was delayed for several months by lawsuits among the sponsors. Ortho Pharmaceuticals was recently granted Treatment IND status for EPO in AIDS-related anemias. This program is currently limited to 30 physicians nationwide. EPO's Orphan Drug status was exploited by sponsors who defined its indications narrowly, knowing the drug will have an enormous market. (One industry insider said "This is bigger than Valium.") It's time to amend the Orphan Drug Act to end such abuses.

EPO could be useful for:

* People who have anemia from taking AZT and need frequent blood transfusions,
* People who have anemia from HIV.

FLUCONAZOLE. Fluconazole is an antifungal drug effective against cryptococcal meningitis and, possibly, candida (thrush). It's taken orally and is less toxic than the IV-administered approved alternative, Amphotericin-B. Fluconazole should immediately be granted treatment IND status.

Fluconazole could be useful for:

* People with acute cryptococcal infections,
* People on cryptococcus maintenance therapy,
* People whose candidiasis (thrush) does not respond to ketoconazole (Nizoral).

FOSCARNET. Foscarnet is a broad-spectrum antiviral with in vitro activity against herpes, Epstein-Barr, shingles, CMV and, possibly, HIV itself. In the US it is being tested mainly against CMV. Like DHPG, it is administered IV, but unlike DHPG, it is not bone-marrow suppressive. So it can be taken along with AZT. Its sponsor, Astra, restricted compassionate use to people who already have life-threatening septic infections from DHPG-induced low white counts.

Foscarnet could be useful for:

* People who cannot tolerate DHPG because of low white blood cell counts,
* People who want to treat their CMV while staying on AZT,
* People who fail on DHPG,
* People whose CMV becomes resistant to DHPG,
* People whose herpes becomes resistant to acyclovir.

GM-CSF (GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTORS). GM-CSF, a genetically engineered version of a naturally-occurring human enzyme, causes proliferation of 2 vital types of white blood cells. Low white cell counts can cause life-threatening bacterial infections. GM-CSF can reverse the bone-marrow toxicity of drugs like AZT, DHPG or cancer chemotherapy, enabling subjects to take treatments which can extend their lives. GM-CSF should not be taken in the absence of antiretroviral therapy. Some reports indicate taken alone, GM-CSF may accelerate HIV replication.

GM-CSF could be useful for:

- **People whose white blood count (WBC) is too low for them to take AZT or DHPG,**
- **People who develop low WBC on AZT or DHPG,**
- **People whose WBC is too low to take cancer chemotherapy.**

DDC (DIDEOXYCYTIDINE). ddC, a potent nucleoside analogue once considered too toxic for widespread clinical use, has proved acceptable when used in far lower doses, intermittently, or in alternation with AZT. It should be tested widely at these safer low doses. The intermittent and AZT-alternating studies should provide the impetus for creative new strategies of combination antiretroviral therapy.

ddC could be useful for:

- **People who are intolerant of or resistant to AZT.**
- **People who cannot stay on AZT because of concomitant myelosuppressive medications like pyrimethamine, DHPG or Bactrim.**
- **People who are failing on AZT.**

8 TREATMENTS WE WANT TESTED FASTER

The following treatments should be tested faster.

ANSAMYCIN. This antimycobacterial has been available from the CDC for compassionate use treatment of MAI. Recently, however, the FDA told ansamycin's sponsor, Adria Labs, that if it wanted to get the drug approved, it would have to end compassionate use and conduct controlled clinical trials. Why can't both be done together? As a result, ansamycin, one of the least toxic and more effective treatments in the unimpressive armamentarium of anti-MAI drugs, is virtually unavailable. It has been reported to have anti-HIV activity as well.

CD4-EXOTOXIN, CD4-IMMUNOADHESIN. First generation CD4's Achilles Heel is its short half life in the bloodstream-about one half hour. To be effective the drug would have to be injected many times a day. Yet by attaching an HIV antibody (immunoadhesin) or a toxic plant protein (exotoxin) to the CD4 molecule, the serum half-life can be extended to 2-3 weeks, long enough to make this a convenient antiviral treatment. Phase I studies of these 2nd generation CD4s should begin immediately, with studies of first generation CD4 continuing to determine longer-range side effects. Efficacy trials should focus on the more practical, convenient 2nd generation products. The CD4-exotoxin might both prevent HIV from attaching to susceptible cells and kill infected cells.

DDC (DIDEOXYCYTIDINE). In vitro, ddC is more potent than AZT. Early clinical studies showed unaccpetable toxicity, especially with the incidence of irreversible peripheral neuropathy, but later studies, using a lower dose, were more promising. Used in alternation, or in low dose combination, with AZT, ddC may help reduce the risk of viral resistance to antiretroviral treatments. Given the pressing need for new antiretroviral regimens, ddC should be in wider trials at the less toxic lower dose now.

DICLAZURIL. Gastroenterologists are up in arms about the Federal AIDS Program's refusal to put diclazuril into clinical trials for treatment of cryptosporidiosis, a devastating protozoan infection that causes diarrhea. Existing treatments are ineffective. The AIDS Program failed to act on 2 successive protocols to test new agents, spiramycin and diclazuril, against cryptosporidiosis. It was just another omission by the AIDS Clinical Drug Development Committee (ACDDC), which meets only 3 times annually and won't consider diclazuril because the principal investigators didn't send in the requisite number of copies. Concerned with maintaining its own procedural regularity, the ACDDC is blocking promising anti-infective treatments from the clinical pipeline. As with aerosol pentamidine, a private pharmaceutical will have to step in where NIAID feared to tread.

HYPERICIN. Hypericin, an herbal extract, inhibits assembly and budding of viral particles from infected cells. Virus-infected mice survived 23 days untreated, 70 days on AZT, and over 240 days on Hypericin. AZT and Hypericin were found to be synergistic. Hypericin blocks syncytia formation in the test tube. No

toxicity has been observed. The half life in mice and monkeys is 2-3 weeks. Hypericin may be active against herpes as well. Cheap and nontoxic, it is a good candidate for combination antiviral trials.

PASSIVE IMMUNOTHERAPY. Plasma rich in HIV antibodies is extracted from healthy seropositive donors and injected into people with AIDS. Two separate uncontrolled studies in England showed striking clinical benefits, remission of symptoms, and improvements in T4-cell counts. Studies in the US have been delayed by lack of funding. This treatment deserves top research priority.

PEPTIDE T. This sequence of amino acids is designed to block HIV's attachment to the CD4 receptors of HIV-susceptible cells. It penetrates the blood-brain barrier, unlike recombinant CD4, which otherwise is designed to achieve a similar result. Preliminary results from Phase I studies indicate remission of symptoms such as rashes and stabilization or improvement of blood markers. Substantially nontoxic, Peptide T should be in wider efficacy trials.

ANTIRETROVIRAL TREATMENTS

You're going to freeze yourself into one moderately successful drug to treat AIDS.

- Samuel Broder, MD, NCI Director to the FDA at the Lasagna Committee 1.4.89

Too much research is focused on nucleoside analogues and their reverse-transcriptase (RT) inhibitory activity. There are many ways to inhibit HIV, including:

* HIV-antibody boosting (passive immunotherapy, CD4-immunoadhesin),
* Viral binding inhibition (CD4, peptide T, IV dextran sulfate),
* Inhibition of cellular HIV production after cell entry,
* Use of viral proteins that inhibit HIV replication,
* Blocking HIV's protease protein to prevent formation of new virus particles,
* Budding inhibitors which prevent new viruses from leaving the host cell (e.g. Hypericin),
* Selective cell-killing agents which kill only HIV-infected cells (e.g. GLQ223, CD4-exotoxin).

Nucleoside analogues less toxic than AZT should become standard (e.g. DDI). If viral resistance is feared, than an alternating regimen of 2 less toxic RT-inhibitors should be developed. The DDC/AZT alternating regimen is probably too toxic. Once satisfactory less toxic RT-inhibitors are identified, research should focus on combination antiretroviral regimens utilizing the mechanisms described above. Candidates for more effective reverse transcriptase inhibitors include AzdU (azidouridine), AZT-DP, D4T (found less toxic than AZT in lab and animal studies), FLT (found several times more effective than AZT in Swedish trials) and Foscarnet.

PROPHYLAXIS FOR THE MAJOR OPPORTUNISTIC INFECTIONS

The importance, high frequency and relative ease of study of the infectious complications of AIDS should make development of prophylactic measures a high priority.

- Jonathan Gold, MD, Memorial Sloan-Kettering, NYC ATIN 3:4, April 1989

Prevention is easier than treatment. AIDS research waits until possibly avoidable infections become acute and life-threatening before treating them, rather than trying to prevent them in the first place.

Five infections—PCP, CMV, MAI, toxoplasmosis and cryptococcal meningitis—occur in at least 80% of people with AIDS (81% of diagnoses in NYC adults up to 4.12.89, they were found in over 90% of 780 autopsied people with AIDS from Memorial Sloan-Kettering Hospital).
Physicians labor ceaselessly to treat these infections in people with AIDS, yet researchers seem curiously reluctant to seek out effective prophylaxes. When Memorial Sloan-Kettering doctors developed aerosol pentamidine, the AIDS Program wasn't interested in testing it. Eventually a philanthropic foundation and pharmaceuticals LyphoMed and Fisons funded the trials.

If these infections could be chronically suppressed in people with low T4-cell counts, overcrowded hospitals would be freed to treat people with AIDS-related malignancies, wasting and neurological syndromes.

Retrospective and prospective studies of the cumulative incidence of opportunistic infections. What is needed is a study of people with AIDS that includes a complete diagnostic workup at the time of diagnosis. Subjects would receive state-of-the-art prophylactic and therapeutic treatments, and be closely monitored for as long as possible. Such a study would provide useful information about at what point other OIs may develop, outlining the true (hitherto unknown) extent of multiple infections and their trajectory in people with AIDS.

It is especially crucial to conduct such studies with women and people of color. Far too little is known of the unique features of AIDS and the pharmacologic effects of new drugs in women. People of color are systematically underrepresented in clinical trials, and adverse effects are only discovered after marketing. Studies in women and people of color would help develop better treatments for infections which might be HIV-related, but which are not classified by the CDC as AIDS-defining (e.g., pelvic inflammatory disease or endocarditis).

PCP prophylaxis has already been developed. Most people at risk can either tolerate sulfa-based drugs like Bactrim or can take aerosolized pentamidine (AP) once monthly or more. After AP is licensed for marketing, post-marketing studies should be conducted to determine optimal dosage, frequency, and nebulizer modality. Subjects in these post-marketing studies should not have to pay for their participation.

CMV prophylaxis is the next priority. Both investigational treatments for CMV infection, DHPG and Foscarnet, are often toxic. A wealth of anecdotal information suggests that high-dose Acyclovir (ACV), while not effective in treating CMV, may prevent it. Burroughs-Wellcome claims to have completed a study of this in Europe. Where are the results?

Toxoplasmosis prophylaxis is another priority. Existing regimens for toxoplasmosis are often intolerable: pyrimethamine is bone-marrow suppressive; its partner, sulfadiazine, causes allergic reactions in the sulfa-intolerant. Prophylactic regimens could compare low-dose pyrimethamine (Daraprim) with clindamycin.

Cryptococcus prophylaxis should be investigated using Fluconazole (available in the UK) or Itraconazole (available in Mexico). These agents might also be useful in suppressing candida (thrush) and other fungal infections like histoplasmosis or coccidioidomycosis.

MAI prophylaxis is one of the most difficult challenges facing clinical research. MAI organisms are ubiquitous. Disseminated MAI is found in up to 50% of PWAs. Existing combination therapy has dubious results. Perhaps MAI could be suppressed with new agents like amikacin, ansamycin or clofazimine.

Herpes prophylaxis using Acyclovir (ACV) should become standard of care for people with AIDS who are infected with HSV-1 and HSV-2.

Community-based trial centers should focus on prophylaxis and treatment of opportunistic infections.

The Federal AIDS Program has shown little interest in trials for prophylaxis or treatment of opportunistic infections. In New York City on May 30, NIAID Director Dr. Anthony Fauci attributed this to lack of sufficient interest on the part of investigators. This is spurious. Time and again, NIAID's own bureaucracy has proved its lack of interest in anti-infectives. Aerosol pentamidine for PCP prophylaxis and spiramycin or diclazuril for cryptosporidiosis are examples.

Yet the best hope of survival for HIV-infected people is to avoid AIDS-related opportunistic infections and cancers. Community-based trials have already succeeded in gathering efficacy data on the only important AIDS-related prophylaxis to attain FDA approval (aerosolized pentamidine).

Prophylaxis for opportunistic infections would be easy to test in large, non-randomized trials, because progression to infection is easy to measure. The US government should fund community-based organizations to conduct a series of nationwide prophylactic trials. This funding should supplement the existing $6 million grant for community-based AIDS research organizations.

TREATMENTS FOR OPPORTUNISTIC INFECTIONS

The word "untreatable" must be banned from the lexicon of AIDS.

Well-designed, quickly executed trials of prophylaxes for opportunistic infections could make the most common OIs rare within 2 years. Successful results should be rapidly disseminated nationwide. Intensive, focused research on refractory disease in cases when prophylaxis failed could produce better, less toxic, more effective treatments for those OIs.

Treatment protocols should:

- Include active controls whenever 2 or more treatments (approved or investigational) exist for the infection being researched,
- Include dose-comparison regimens whenever the trial drug is the only treatment for the condition being researched,
- Include open-label arms for those who can't take standard treatment (i.e., open-label pentamidine for the Bactrim-intolerant),
- Include state-of-the-art patient care,
- Allow prophylaxis, treatment & maintenance for other conditions.

Antiviral treatments. Does low-dose Foscarnet have broad-spectrum antiviral activity against herpes, shingles, Epstein-Barr virus and CMV? Could Foscarnet be administered orally? What are the prospects for human testing of newer anti-herpes drugs like (S)HPMPA, (S)HPMPC and IPdP?

Antifungal treatments. What are the prospects for low-dose Fluconazole for suppression of cryptococcus, histoplasmosis, candidiasis and other fungal diseases? What about Itraconazole and other new antifungals?

Antibacterial treatments. Existing treatments for cryptosporidiosis are unimpressive. The Federal AIDS Program has shown no interest in Diclazuril, a new antibiotic from Europe. Community-based groups should test this promising substance. Sandostatin, now being tested in Europe, should be tested in the US as well.

New European antibiotics such as roxithromycin and azithromycin have shown promise in vitro and in animal models against cryptococcus, toxoplasmosis and, possibly, MAI. They should immediately be tested in Americans.

MAI is usually resistant to existing treatments. Most clinicians indiscriminately use a combination of 3 or 4 anti-tuberculosis drugs. These have little impact. New trials must assess which anti-TB drugs are effective. Because mycobacteria rapidly develop resistance, treatment strategies should always use 2 or more agents, and should consider switching agents if initial combinations don't produce improvement within 6-10 weeks. New agents like liposome-encapsulated amikacin, ansamycin and clofazimine deserve consideration.

Blood conditions. EPO and the CSF's should be available now. They improve AIDS and cancer chemotherapy, providing improved quality and length of life. Other blood-cell growth factors need to be identified. New cytokines which improve cell function should be developed.

Some clinicians now treat AIDS as a blood disorder. Treatments need to be developed which protect the bone marrow not only from HIV but from the toxic effects of drugs such as AZT, DHPG and pyrimethamine. Burroughs-Wellcome's folinic acid (leucovorin/Wellcovorin) is of some use in this, but it is as absurdly overpriced as AZT.

Many people with HIV have enlarged, dysfunctional spleens. Neither surgery, radiation nor chemotherapy is adequate to restore spleen function. Low platelet levels (thrombocytopenia) are another chronic HIV-related condition. It could be a direct result of HIV, a result of OIs such as MAI, of spleen dysfunction, or of auto-immune antibodies which attach to platelets, making them dysfunctional. There should be comparative trials using substances like AZT, EPO, gamma globulin, prednisone or vincristine for people with thrombocytopenia.

Syncytia are clumps of dysfunctional immune cells attached to an HIV-infected T4-cell. Circulating immune complexes (CICs - antibodies attached to antigens) damage tissue in some people with AIDS. Plasmapheresis is an expensive mechanical method of eliminating CICs from HIV-infected people's blood. Is there a cheaper chemotherapeutic way to achieve this? Can IV-dextran sulfate inhibit syncytia formation without exposing subjects to the risk of uncontrolled bleeding?

GI and Wasting Syndromes. For too long, wasting has been regarded as untreatable. Many conditions now diagnosed as "HIV wasting syndrome" may, in actuality, be GI infections like MAI, which some AIDS clinicians are too busy or disinclined to aggressively diagnose and treat. A cancer drug, megestrol acetate (Megace) is now being tested to treat AIDS-related wasting syndromes. The optimal dosages need to be found. Both appetite and absorption need to be improved.

Neurological conditions. Treatments are seldom satisfactory for neurological complications of AIDS, from direct HIV-encephalopathy to malignancies like lymphoma, opportunistic infections like toxoplasmosis and non-AIDS specific conditions like encephalitis (common in IV-drug users with AIDS). Diagnostic procedures are often nonspecific or else invasive. The full role of HIV in the brain is ill-understood. Treatments for brain infections like toxoplasmosis and cryptococcal meningitis should satisfactorily cross the blood-brain barrier.

Malignancies. Available treatments for Kaposi's sarcoma and the several AIDS-related lymphomas are unsatisfactory. Some doctors feel the optimal approach would be to inhibit HIV before it leads to such malignancies; others use traditional, often highly toxic chemotherapeutic or radiation treatments that have limited efficacy. The etiologic role of Epstein-Barr Virus (EBV) in certain AIDS-related lymphomas needs to be explored and treatments developed.

Immunomodulators. Other than proven blood-boosters like EPO and the colony stimulating factors there has been little progress in this area. Dr. Fauci thinks alpha interferon may be both an immune booster and an antiretroviral in less immune-suppressed individuals. Others think alpha interferon levels, which rise as progression to AIDS takes place, may be an immune downregulator. NIAID is testing IL-2 as an immune booster, but one study showed that IL-2 treated subjects progressed faster than untreated controls. Naltrexone & other opiate antagonists or endorphin stimulants are equally ill-understood.

Addiction treatments. In IV-drug users and those addicted to cocaine or crack, drug addiction should be treated as the primary infection, with HIV and OI therapy as an adjunct. Methadone is an imperfect treatment for opiate addiction. It perpetuates the underlying addiction and allows users to continue using cocaine or speed. No effective chemotherapy exists for cocaine or crack addiction. Agents under investigation include carbamazepine, brupenorphine, bromocriptine, imipramine, desipramine and flupenthixol decanoate. The best treatment seems to be acupuncture, which also may have immune-boosting effects, and is more popular than methadone among many drug users. Combination regimens of acupuncture and chemotherapeutic alternatives to methadone should be explored.

Alternative and underground treatments. Immunosuppressed people frequently use alternative, holistic and complementary treatments. San Francisco's County Community Consortium (CCC) has taken a positive step by recognizing these and prospectively assessing their efficacy in its Alternative Treatment Database. An integrated approach to evaluating real-world options for AIDS treatments would acknowledge the existence and possible utility of complementary treatments. It would seek to identify and disseminate the most useful agents.

A striking proportion of new AIDS treatments are derived from plant proteins like Carrisyn (aloe vera), Lentinan (a Japanese mushroom), Butyl DNJ (deoxynojirimycin-akin to castanospermine and being tested in ACTG 100), hypericin (St. John's wort), and GLQ223 (trichosanthin). In vitro assays of plant proteins for anti-HIV and anti-infective activity should be accelerated, with promising substances being tested in humans as quickly as possible.

V. AIDS DRUG DEVELOPMENT DISASTERS

> **The time is ripe to proclaim and implement a new mission for the FDA—to speed the public's access to important new drugs. No change in the law is needed to do this—simply acceptance of the fact that past approaches have not served the public well enough.**
>
> **- Louis Lasagna, MD, "Will All New Drugs Become Orphans?"**

The following is a brief list of AIDS treatments whose development illustrates problems in the clinical trial status quo. DDI, EPO, Fluconazole, Foscarnet, GM-CSF, Passive Immunotherapy and Peptide T also exemplify problems with drug development, but they have been covered in Part III. Inclusion in this list is not an endorsement of the treatment.

Aerosol pentamidine. Over 30,534 Americans have died of AIDS-related PCP. Yet as long ago as 1977, Bactrim was known to prevent PCP (CDC AIDS Weekly Surveillance Report, 2.20.89 and 9.5.88, "Successful chemoprophylaxis for Pneumocystis carinii pneumonia," N Engl J Med 1977; 297:1419-1426; "Remarks" of Michael Callen, FDA Hearings, 5.1.89). People with AIDS were rarely prophylaxed against PCP, however, because of poor-quality clinical research into opportunistic infections. Doctors in New York and San Francisco began testing aerosolized pentamidine (AP) for PCP prophylaxis in 1986, but the Federal AIDS Program waited another 13 months before starting its trial. 16,929 of the total PCP deaths occurred since AIDS activists first asked Dr. Fauci to begin trials. (CDC; Callen, ibid.). When NIAID finally began its trial (ACTG 021), it was placebo-controlled. No one signed up. The trial was redesigned, the placebo eliminated, and in the meantime, community trial groups in San Francisco and New York conducted research which led, in February 1989, to treatment IND. In May 1989, FDA's advisory committee recommended full approval for AP. To conduct the community-based trial, the sponsor, LyphoMed, raised the price of its IV-pentamidine by 300% to $100 a vial, highlighting abuses of the Orphan Drug Act during the AIDS crisis.

Ampligen. A putative antiretroviral, ampligen was initially given high priority by the AIDS Program, but took a year to "thread its way through the many stages of protocol development and approval." (AIDS Drugs:

Where Are They?). Many people clamored for the drug. Phase II trials failed to show benefit. The trial was halted. 12 of 20 in the Ampligen-treated group progressed, while only 8 of 20 in the placebo group did so. It is unclear whether this difference is statistically significant. The inventor, HEM Research Inc., and its pharmaceutical partner, DuPont, had a falling out. DuPont sued HEM and HEM fired its president. At this late date, the FDA chimed in, claiming the drug was never described pharmacologically. If so, the FDA shouldn't have allowed HEM/DuPont to conduct the efficacy trial in the first place. (The same tardy oversight occurred with Imreg-1). One charge that emerged in the corporate dispute was the claim that a wealthy Texan with AIDS was asked to lend HEM $1 million in return for a place in the trial. Trial subjects should never have to pay, directly or indirectly, to participate in trials.

AZT. Developed largely at public expense, its revenues have been privatized in the hands of Burroughs-Wellcome, impoverishing most people who take it. Considered too toxic even for cancer chemotherapy when first discovered in 1964, it was approved for AIDS at a dose so strong most users became transfusion-dependant or stopped taking the drug. In AZT's expedited approval, crucial questions were overlooked: Why was such a toxic dose recommended? Can a drug which drives many people into poverty be considered "safe"? How many other companies will exploit the Orphan Drug Act and profiteer off the bodies of people with life-threatening disease? The FDA revised its Treatment IND program on the basis of its experience with AZT, but no drug since has received the same wide distribution AZT got before marketing approval. The Federal AIDS Program's clinical trial pipeline is still clogged with AZT trials, more than 2 years after approval.

CD4. Several companies are competing intensely to develop various CD4 products, but the pace of this well-publicized drug's clinical development remains agonizingly slow. In their haste to be the first on the block, Genentech failed to keep up with the published literature on the proper chemical sequence of the CD4 protein receptor, and the Genentech product in Phase I trials turned out to have the wrong amino acid at one end of the molecule. The company blandly assured that all was well, the wrong molecule might work just as well as the right one. This is bad science, a waste of resources and a ripoff of trial subjects and their hopes.

Dextran sulfate. Approved in Japan for coagulation disorders, dextran sulfate was obtained on the underground market by hundreds of people with HIV as a possible antiviral. After wasting almost a year, the AIDS Program started a trial. It neglected to figure out whether the oral form was absorbed. There was no assay to measure dextran sulfate's penetration into the blood. The trial indirectly showed oral dextran doesn't reach the bloodstream. Advocates wonder if the trial was designed to fail because researchers were irritated by the alternative network that espoused dextran sulfate.

DHPG (ganciclovir). Approved for anti-CMV therapy in Europe, DHPG's US trials were delayed by a patent dispute between Syntex and Burroughs-Wellcome. The reluctance of pharmaceuticals to let drugs out under compassionate use is the direct result of the FDA's 1987 rejection of DHPG. Doctors were unwilling to give people a placebo because untreated CMV retinitis leads inevitably to blindness, and there were no alternatives. In December, 1988, FDA, the AIDS Program and Syntex started 3 new trials of DHPG: compassionate use, treatment IND, and a delayed-treatment control. This produced an immediate outcry from the AIDS community. The new trials coerced subjects into the delayed-treatment controlled trial. Only 5 subjects signed up. ACT UP held demonstrations. NIAID's Dr. Fauci told Congress DHPG should be approved. The FDA relented and reopened the compassionate use program. In May 1989, the FDA's advisory committee recommended DHPG for full approval. This was the first time a drug was recommended on the basis of overwhelming clinical experience rather than on controlled trials.

Imreg-1. Derived from human plasma, Imreg-1 is claimed by its developer to be an immunomodulator and an antiviral. FDA maintains the drug is ill-characterized and perhaps immunologically inert. "Seduced and abandoned" by mixed messages from the FDA, the hapless sponsor, Imreg, Inc., was punished in November, 1988 for daring to apply for treatment IND without enough efficacy data. Yet for months FDA Commissioner Frank Young had beseeched companies to apply for treatment IND. This underlined confusion about the program: was treatment IND intended to be a real trial, applicable to drugs with the possibility of efficacy, or was it a bridge to approval, a quasi-NDA, with access only granted to treatments slated for full approval?

IVIG. Intravenous immunoglobulin is derived from pooled plasma. Some researchers feel that it helps immunodeficient children resist bacterial infections. The IVIG trial of children with AIDS was designed with an unusual placebo. Not harmless, the intravenous placebo was intended to expose the control group to infections at the injection site that the treatment group was supposed to be protected from. Informed consent forms failed to explain this chilling rationale. Parents and guardians of children are sometimes coerced into allowing their wards into this trial with the promise of better health care. Considering the abject state of health care for most children with AIDS, this promise is probably accurate, but still unethical.

Trimetrexate. Trimetrexate is 1500 times more active than Bactrim against a key enzyme of the PCP organism. It was the first AIDS-related drug granted treatment IND status. This turned out to be a Pyrrhic victory. FDA restricted the treatment IND trial to people who had severe adverse reactions to both IV-pentamidine and TMP/SMX (Bactrim). Failure to respond to those treatments was not enough. Patients had to be virtually

dead to qualify for trimetrexate, which skewed results against the drug. Only 89 people got into the treatment IND. Others died because approved treatments for PCP did not work on them, but were not actually toxic. What was toxic was the FDA's refusal to allow more people access to trimetrexate until it relented under pressure from the Lambda Legal Defense & Education Fund in summer 1988. Partly due to the delays, Warner-Lambert is considering dropping its IND altogether. Another promising drug may be permanently unavailable due to FDA malfeasance.

CONCLUSION

Last summer FDA Commissioner Frank Young attempted to justify the lack of promising new treatments for AIDS, saying "We can't approve something that isn't there." He predicted that no more than 2 new drugs would be approved for AIDS-related conditions by 1991.

Thanks to unrelenting pressure by AIDS advocates, Young's prediction proved false. In the last year, alpha interferon was approved for treatment of Kaposi's sarcoma, aerosolized pentamidine and DHPG (ganciclovir) were designated as treatment IND drugs and recommended for full FDA approval. EPO is on the verge of approval as well.

Humane, well-designed, quickly-executed clinical trials conducted by San Francisco's County Community Consortium (CCC) and New York's Community Research Initiative (CRI) produced data for approval of aerosol pentamidine. This was the most important single therapeutic advance for AIDS since 1981. In the meantime, the Federal AIDS Program has continued conducting its endless, unproductive protocols.

AIDS advocates have identified the systematic problems afflicting the scientific and regulatory body politic. The point is to solve them. As citizens of this country, we have the right to demand that our government deploy its resources to save the most lives right now. Those with the power to redirect our nation's AIDS research effort must listen to and work with us. We will not rest until they do so.

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