FACTS ABOUT EXPERIMENTAL AIDS THERAPIES

More than 100 drugs have been screened to find substances effective in treating AIDS or AIDS-related conditions, including: 1) antivirals, which may act against the HTLV-III virus; 2) immune modulators, that might bolster the immune system; 3) combinations of therapies; and 4) drugs that might be effective against AIDS-related "opportunistic" infections.

Clearing a drug for use is a careful procedure. When a substance shows promise in laboratory testing, a manufacturer seeks FDA Investigational New Drug (IND) approval for human testing: for safety on a small number of persons, then for both safety and effectiveness on a larger group, including AIDS patients. If these trials are successful, wider human testing is conducted. If the drug passes all these tests, FDA gives its approval to a New Drug Application (NDA) for marketing.

Drugs marked * have approved INDs; those with ** have approved NDAs.

Antivirals: Ansamycin; BW A509U (Compound S)*; Foscarnet (phosphonoformate); HPA 23* ; Virazole (ribavirin)*; and Suramin.*

Immune Modulators: Alpha interferon* ; IMREG 1* ; Interleukin-2* ; Isoprinosine.*

Combination Therapy: Interleukin-2 + Suramin + Bone Marrow Transplantation; Interleukin-2 + Suramin + Alpha interferon.

Opportunistic Infections

- For Pneumocystis carinii pneumonia (PCP): Pentamidine**; trimethoprim-sulfamethoxazole**; DFMO (alpha difluoromethylornithine)*; Fansidar*.
- For Cytomegalovirus: DHPG (9- 1,3 dihydroxy-2-propoxymethyl guanine)*; Foscarnet.
- For Cryptosporidiosis: DFMO*; spiramycin*.
- For Kaposi's sarcoma: Alpha interferon; single agent and combination chemotherapy; radiation therapy.
- For Mycobacterium avium-intracellulare: Ansamycin*; Ansamycin and clofazimine*; rifampin.*

Future Treatment Efforts:--No effective AIDS therapy now exists. Antivirals offer promise, but, so far, none has been found to have a significant effect against AIDS in humans.

Future success could lie in aggressively attacking the disease early by combining antivirals and immune stimulators. To achieve effective therapy, carefully controlled clinical studies, which insure maximum safety and effectiveness, will be needed as well as more multicenter groups to perform the studies.

iads strategy Garrett ME 9/i/87

Suggested Intro:

A small but ~~elect~~ select group of scientists are ~~gathering~~ gathered in Washington this week to discuss a national strategy for attacking the AIDs virus. The meeting, which was organized by the National Academy of Sciences, opened on a pessimistic note. NPR Science Correspondent Laurie Garrett has more.

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There is growing skepticism it will ever be possible to get the human immune system to fight off the AIDs virus,

AIDS researcher William Haseltine, of Harvard University, opened the meeting ~~with a somber tone.~~ saying it is highly unlikely ~~said Haseltine,~~ a vaccine against AIDs will be developed in the next ten years. So we have no choice, ~~as a nation,~~ said Haseltine, but to turn to drugs ~~for treatment~~ instead of vaccine, for prevention of AIDS. Haseltine called for a national campaign to identify the most promising drugs, test them, and put them in clinical trials. It is simple and logical, said Haseltine. Drugs would be found to both treat & prevent AIDs. There are ten key proteins in the AIDs virus ~~es~~ --- that means there are ten key targets for antiviral drugs. ~~Ten agents upon which we can draw our biochemical weaponry.~~

The idea is to develop an anti-AIDs drug that could be taken regularly the same way travelors take chloroquine every day to protect them from malaria, Haseltine said.

A ~~"I outlined here.....national capacity."~~ "I recently heard... that single effort."

So Haseltine thinks 500 scientists should be coordinated into teams of 50 each analysing one of the key proteins of the AIDs virus,

Haseltine said the only immediate hope in the war on AIDS lies with finding and developping a drug that can be taken regularly by people who are infected with the virus. ~~He called it chemoprophylaxis ---- using drugs to prevent the virus from causing AIDS.~~ This, said Haseltine, In some parts of the world where over 5% of the adult population is already infected with the virus, every sexually active adult might be put on such drugs. It is the only way to

stop the epidemic. Nobel Laureate David Baltimore, of the Massacusetts Institute of Technology, said he was sympathetic with Hsaeltine's ideas. But he felt they were impractical.

A "It's very unlikely.....le-ser developed world."

To which Haseltine responded ---

A "It is implicit.....national goal."

But exactly who defines our natonal goals in the war on AIDS remains unclear. Only one member of the President's Commission on AIDS, Frank Lilly, is attending the meeting so far, he has reserved comment. Anthony Fauci, director of the national Institute of Allergy and Infectious Disease, outlined a complex web of federal agencies, coporate officers, and universities around the country involved in AIDS research. But nobody seems to be at the top. David Baltimore charged the scientists are duplicating each others efforts, he said, and the battle against AIDS is being slowed by ego fights between scientists, the unwillingness of many to share vital laboratory samples, and the lack of a clearly coordinated national research effort. Baltimore called for a centralized AIDs masterplan ---- federal leadership of academic, government and corporate AIDS research. Without such a strategy, argued Baltimore, our epidemic will grow to astonishing proportions, while scientists stand by fighting over drug developments and profits.

A "I believe in a national.....will be compromised."

David Barry, of the Burroughs Wellcome Company, was

talk of increased federal oversight of corporate research.

not pleased with ~~such discussion.~~ Burroughs Wellcome manufactures the only drug ~~in legal~~ authorized for use against AIDS -- AZT. Annual treatments for AZT run about $]0,000. ~~and it is the high cost of the drug that has prompted so much debate about our nation's AIDS campaign.~~ Barry defended the cost, saying his company spent over $200 M developing and testing AZT before it was marketed. Any other AIDS drugs will require ~~such an~~ similar investments. ~~[illegible]~~

Barry suggested the Federal Government look to Japan as a model for drug development. There, the government directly subsidizes pharmacuetical companies, paying much, if not all, the costs of drug research and development. Only through such subsidization, said Barry, can the prices of drugs be held down.

The meeting will continue today, with ~~debate over~~ discussion of the ethics of testing drugs on ~~AIDS patients and~~ people infected with the AIDs virus, & AIDS patients.

In Washington, I'm Laurie Garrett.

AIDS MEETING IN WASHINGTON ME GARRETT 9/2/87

Treatment

SUGGESTED INTRO:

A SMALL GROUP OF THE NATION"S TOP HEALTH EXPERTS AND ADMINITRATORS GATHERED THIS WEEK INWASHINGTON TO DISCUSS STRATEGIES FOR DEFEATING THE AIDS VIRUS. THE MEETING ENDED IN FRUSTRATION, WITH NO CLEAR PLAN. NPR SCIENCE CORRESPONDENT LAURIE AGRRETT HAS MORE.

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There is only one drug legally available to AIDS patients right now -- AZT. At least 10% of all AIDs patients can't tolerate the drug --- some estimates ~~it~~ put that figure as high as 30%. And ~~even~~ for those who can tolerate the drug, it is not ideal. At best, AZT buys AIDS patients some months, and limits the amount of suffering they face. Everybody involved in AIDS research is anxious to find a cure for the disease, or at least a better treatment. There ~~are~~ is a list of about 80 drugs now in various stages of development, ~~worldwide. Some may soon go into clinical trials.~~ That sounds encouraging. But Martin Rosenberg, of Smith Kline/~~and French~~ Beckman, a pharmaceutical corporation, says very few of the ~~80~~ drugs on that list look at all promising.

side affects of the

A "Most of these....of a new drug."

At the moment, 90% of all the resources of the federal clinical ~~drug~~ AIDs testing program are being put into AZT trials. The National Institutes of Health and the Food and Drug Administration want to refine the use of the drug. ~~Some scientists charged at this week's meeting that the NIH financial commitment to AZT tests is misplaced. As~~

Nobel Laureate David Baltimore, of MIT, charged NIH's commitment to AZT work is misplaced. put it, why not let AZT manufacturer Burroughs Wellcome do all those tests, said Baltimore, it's a big copoation. And it stands to make big profits. NIH, said Baltimore, should be concentrating on other drugs. NIH officials said they are beginning to test some of the other drugs on the list. ~~other drugs, notabely ddC, which is similar to AZT, and AL-721.~~ But the sad irony is that these drugs are already being used by AIDS patients -- illegally. Barry Gringell, of Gay Men's Health Crisis, told the meeting AIDS patients are increasingly desperate and frustrated with the slow pace of AIDS drug development and testing. So they are getting drugs from the AIDs black market.

~~A "There is a vast.....dext-asulfat."~~ as he spoke

But drug testing, it turns out, is necessarily a slow process. To get valid information about the safety and usefullness of a drug, doctors must carefully set up clinical trials that involve large numbers of patients. And some of the patients must receive a control substance -- something scientists can compare their new drug to. Usually that control substance is something useless, a placebo. But AIDS patients refuse to take placebos, and many doctors think the use of a placebo in the case of AIDS is immoral. So the FDA has approved the use of AZT as a control substance. All drugs will, therefore, be compared to AZT. Barry Gingell argued that was

Patient advocate Barry Gringell charged AZT manufacturer Burroughs Wellcome is not making the drug available for use as a control in other drug tests. A Burroughs Wellcome spokesperson denied the charge, but admitted there have been delays in getting AZT supplies to researchers involved in clinical trials.

But drug testing, ~~it turns out,~~ is necessarily a slow process. Martin Hirsh, of Massachusetts General Hospital, outlined the steps involved in setting up ~~clinical~~ trials of AZT, ~~among AIDs paitents with brain diseases.~~ It took ten months, he said, to ~~get~~ jump all the legal and bureaucratic hurdles. ~~to get such a trial started.~~ But Hirsch thinks that trial was set up as fast as is ~~humanly possible~~.

A "If we take shortcuts....none at all."

Somehow, said Hirsch, ~~we have~~ to make the AIDS population understand that all this is necessary. ~~We are moving as fast as we can.~~ There is no conspiracy, he said, to slow things down or zero in on any one drug. Hirsch added that Massachusetts General, one of the nation's largest hospitals, already feels overwhelmed by the number of ~~drug~~ trials it is involved in. ~~"We can't take any more AIDS trials, " said Hirsch, "Without additional facilities and personnel. That sentiment was echoed by representatives of several of the nation's leading AIDs research centers~~. Jerry Friedland, of Montefiore Hospital in New York, said ~~there aren't enough doctors and nurses in the United States today trained~~ to conduct proper drug trials. ~~We~~ simply can't meet the demands of the AIDs epidemic.

A ~~"Clinical trials.....~~

Many scientists called for creation of some type of ~~centralized~~ AIDS research command post. Some company representatives cringed at the concept, expressing concern they would be ~~pushed~~ to follow federal dictates. One industry scientist suggested the government create a central respository for samples of key chemicals and biological products useful in AIDS research. ~~Another suggested the National Academy of Sciences set up an oversite commission to coordinate the activities of industry, academia and government in AIDS research~~. Noteably, nobody mentioned the Presidential AIDS Commission, and it was clear none of these scientists feel that body can or will play a vital role in directing the future of the AIDS epidemic. The only hopeful note in this meeting was sounded by FDA Commissioner Frank Young, who declared AIDS the number one priority of the FDA. ~~Young said the FDA is doing everything possible to streamline drug approvals for AIDS, and is working closely with industry and researchers to find anti-AIDS drugs.~~

Garrett/ 3

A "There will always....war on AIDS."

Despite repeaded calls for closer cooperation between industry, basic science and government, the meeting ended on a sour note. A proposal to create a government-run repository of chemical and biological materials met with complaints from drug manufactureres. They said their patent privileges might be compromosed x by disclosing what chemicals and biological products they are working on in their AIDS research.

In Washington, I'm Laurie Garrett.

~~Unfortunately~~, The meeting ended with no ~~result~~ consensus about the strategy for AIDs. ~~As scientists left, each was returning to their~~

And the corporate, academic and government scientists ~~left~~ departed to fight AIDs, without any coordinated leadership.

In WA, I'm LG.

National Institute of Allergy and Infectious Diseases

Treatment

Backgrounder

NIAID AIDS CLINICAL TRIALS PROGRAM

Q. What are the goals of the NIAID AIDS Clinical Trials Program?

A. NIAID established the Clinical Trials Program to conduct collaborative clinical trials of experimental therapies in persons infected with the human immunodeficiency virus (HIV). The goals are (1) to provide timely information to guide physicians in selecting the most appropriate therapy, (2) to ensure that questions of the highest scientific priority are answered, and (3) to develop new agents from preclinical studies to final FDA approval.

Q. Who is involved in this program?

A. NIAID has enlisted many outstanding clinical researchers whose broad scientific expertise is focused on the diverse manifestations of AIDS and AIDS-associated conditions. These investigators are part of the AIDS Clinical Trials Group (ACTG), a standing organization that can continuously develop and carry out the highest priority, multidisciplinary clinical trials.

Q. Who else is involved in this Clinical Trials Group?

A. A second part of this cooperative group is the Clinical Trials Coordinating Center, which uses a computerized data base system to rapidly pool and analyze data, and closely monitor studies in progress. The third part of this Group is the NIAID AIDS Program, which allocates resources and provides logistical support. The Group also receives input from other researchers, industry, the Food and Drug Administration (FDA), and the public.

Q. Where are the clinical trials conducted?

A. The trials are conducted in AIDS Clinical Trials Units (ACTU's) located in 15 states and the District of Columbia. Some of these Units were originally funded as AIDS Treatment Evaluation Units (ATEU's) and others were funded as AIDS Clinical Study Groups (CSG's).

Q. What prompted the organizational change to ACTU's?

A. The changes were recommended by an ad hoc Clinical Trials Advisory Panel that met in 1987 to review the NIAID AIDS Clinical Trials Program. The panel recommended that, in order to more quickly meet the goals of the Program, a cooperative group be established with ATEU's and CSG's as full partners having increased responsibility for protocol development and implementation.

Q. **How are drugs chosen for study in the ACTU's?**

A. Information on a promising substance can be submitted by investigators or pharmaceutical sponsors directly to the ACTG or to the AIDS Clinical Drug Development Committee (ACDDC), an NIAID advisory body that includes distinguished scientists from NIH and academic research centers. Following review of the data for a candidate drug, the ACDDC assigns priorities for further clinical testing by the ACTU's in specific populations. Agents may be proposed for potential use against HIV infection or against the various opportunistic infections and cancers that develop in HIV-infected persons.

Q. **How are protocols developed for the ACTU's?**

A. A protocol concept sheet can be submitted by individual ACTU investigators, NIAID staff, pharmaceutical sponsors, or others to the AIDS Clinical Trial Program Operations Office. The concept sheet outlines the rationale and objectives of the protocol, study design, eligibility criteria, treatment regimen, sample size estimate, and logistical estimates.

Q. **What happens to the protocol concept sheet after submission?**

A. The concept sheet is submitted to the appropriate research committee of the AIDS Clinical Trials Group, which evaluates the concept, and if it believes the study is of high priority, appoints a protocol team. The chairman of this team oversees development of the protocol, with input from the AIDS program, other investigators, the pharmaceutical sponsor and the FDA. The final protocol is reviewed by staff of the AIDS program. The committee also identifies participating ACTU investigators. The final protocol must by approved by the local Institutional Review Board (IRB) for each participating ACTU. Upon approval, the protocol is activated and recruitment of volunteers can begin. In many randomized studies, an independent Data and Safety Monitoring Board is responsible for interim data review.

Q. **How much time does it take to develop a protocol?**

A. It depends on the size and complexity of the study. A phase III efficacy trial is more complex and the protocol would take more time to develop than a phase I pilot study, which is simpler and would require less time. Other factors may delay initiation of a study. These include major design revisions late in protocol development, problems with drug supply, special drug packaging requirements, delayed FDA approval, or delayed IRB approval at local institutions.

Q. **How many persons are included in a clinical trial?**

A. Generally, the numbers enrolled depend on the purpose of the specific study. Phase I trials, which determine safe dosage and possible toxicity of a drug, usually involve small numbers of persons. Phase II studies may involve up to several hundred persons and provide more information about safety as well as some indications of efficacy. Phase III trials are even larger; they are

intended to ascertain precisely a drug's effectiveness, safety, and most desirable dosage. In Phase II and Phase III trials, the experimental drug may be compared with a licensed drug, another experimental drug whose actions are known, or an inert substance called a placebo. These studies are typically "double-blinded;" i.e., neither the investigators nor the volunteers know who is receiving which substance.

Q. **Why are placebo-controlled, double-blinded trials necessary?**

A. Such studies are the most scientifically precise and efficient way to determine whether an experimental drug is producing a particular effect or whether the results are due to variables or to chance. Furthermore, placebo-controlled, double-blinded trials are highly ethical and humane because statistically sound proof of efficacy can be demonstrated in small numbers of people within a relatively brief time.

Q. **Do all the ACTU's do the same studies, and in the same way?**

A. One, several, or all of the ACTU's may participate in a specific study, depending on the protocol design and the study population available. All procedures in multicenter studies are standardized, including patient evaluations, use of specialized instruments, laboratory techniques, handling of drugs by hospital pharmacies, and data management.

Q. **How are the results of multicenter trials coordinated?**

A. The NIAID awarded a contract in September 1986 to Research Triangle Institute, Research Triangle Park, NC, to set up the AIDS Clinical Trials Coordinating Center (ACTCC). The ACTCC performs all field monitoring, data collection and storage, and statistical analysis functions that would be the manufacturer's responsibility in a company-sponsored trial.

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