

# European AIDS Treatment

# NEWS

Volume 3 Number 6

## STATEMENT OF PURPOSE

The **European AIDS Treatment News** is a bimonthly publication issued by the **European AIDS Treatment Group e.V. (EATG)**. The EATG is a group of activists from thirteen different European countries and a growing number of associates who participate in treatment activism, community-based research and treatment training programmes.

EATN reflects this by giving information on:

- \* **basic medical knowledge**
- \* **research results and issues**
- \* **treatment news**
- \* **treatment activism in Europe**

EATN invites you to copy or translate parts or all of it. We kindly ask you to send us any translations as we may make use of it through our network.

## IMPRESSUM

### European AIDS Treatment News

Editor: Matthias Wienold, Hannover  
News Editor: Stephan Dressler, Berlin  
Kees Rümke, Amsterdam

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EATN  
c/o Archiv für Sozialpolitik  
Brönnertstr.9  
D-60313 Frankfurt/Main

## EDITORIAL

### Dear Reader,

just to remind you of the questionnaire you received with the last two issues of EATN. Please help us to improve the quality (and funding) of this newsletter by completing it. We are keen to know what you think of EATN and how you use it.

The latest news is that Glaxo and Wellcome are really going to merge. In several countries the companies are now discussing what consequences this may have for the strategy and marketing in the AIDS-field. This seems to be a very important occasion for community treatment activists to approach both companies and insist on the „patient population's“ voice being heard in planning future activities.

The news-section of this issue carries two interviews. Dr. Kunze, a German immunologist, answers questions referring to enzyme therapy in HIV infection. Another interview is covering the issue of physical exercise as an adjunct to HIV-therapy.

EATN-special is committed to the documentation of a statement by Hoffmann-La Roche, Basel, in response to protests by the French TRT5 group against the way the Invirase (saquinavir) trials are being conducted (also see EATN 3.1 and 3.3)

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# Treatment News update

## News from EATG

Since the first of April, Rodya Troyke is EATG's new secretary in Berlin. Rodya, medical student in Berlin, replaces Michael Kruppa who left his job at the end of March. Good luck, Rodya!

### AIDS and Medication conference rescheduled

To account for various difficulties in the preparation of the annual conference of EATG the board of directors has decided to reschedule the AIDS&Medication meeting to late July. The meeting will be held in Lisbon, Portugal and will be in close connection with the Consensus Symposium on Antiviral Therapies to be held there. For more detailed information please contact the secretariate of EATG.

## Substances

### Interleukin-2

An efficient immunomodulating therapy for HIV infection has long been a desire. So far only few substances have undergone clinical trials, and due to the difficult pathogenesis of HIV infection, progress in the field of immunomodulating substances has been rather slow. Some more data are available now. According to an article published in March 1995, 25 HIV-infected patients were treated with interleukin administered as a continuous infusion at a dosage of 6 to 18 million International Units (IU) per day for 5 days

every 8 weeks during a period of 7 to 25 months. In 6 of 10 patients with base-line CD4 counts higher than 200 per cubic millimeter, interleukin-2 (IL-2) therapy was associated with at least a 50 percent increase in the number of CD4 cells. IL-2 therapy resulted in a decline in the percentage of CD6 lymphocytes expressing HLA-DR and an increase in the percentage of CD4 lymphocytes that were positive for certain proteins of the IL-2 receptor. 4 Patients had a transient but consistent increase in the plasma HIV RNA level at the end of each infusion. In the remaining 15 patients, who had CD4 counts of 200 or fewer cells per cubic millimeter, IL-2 therapy was associated with increased viral activation, few immunological improvements and substantial toxic effects (including rash, fatigue, fever, muscle pain, and others). This study indicates that there might be some benefit from IL-2 treatment, but further studies are required for a proper evaluation of this therapy. At least, this study should encourage other investigators to look into the potential of immunomodulating substances - also in Europe. The potential of immune-based therapies was also outlined in a review by M. M. Lederman. Lederman says that properly designed trials of host-directed and immune-based therapies can provide key insights into pathogenesis of HIV disease that may be otherwise unattainable through in vitro studies. More emphasis must be placed on immune-based therapies.

Kovacs, Joseph A. et al.: Increases in CD4 T-lymphocytes with intermittent courses of interleukin-2 in patients with HIV infection. *New England Journal of Medicine* 1995; 332; 567-575

Lederman, M. M.: Host-directed and immune-based therapies for HIV infection. *Annals of Internal Medicine* 1995; 122; 218-222

## Enzymes in HIV Infection

The use of hydrolytic enzymes in HIV infection has remained a controversial issue. The Germany-based drug company Mucos, producer of several enzyme products, has conducted some short-term clinical trials of which the results are not yet conclusive. The number of patients included in these trials is low, and results often show no significant difference to control groups, receiving no enzyme therapy. However, as a consequence of the increased awareness towards immunological aspects in the pathogenesis of HIV infection (fostered by the work of Levy and others), immunomodulators have recently gained more attention. The possible immunomodulating action of enzymes was discussed briefly by Uli Marcus in EATN (Vol. 3, Nr. 2, p. 17). For the time being, it is unclear whether long-term use of enzymes may result in clinical benefits for HIV-infected persons.

### Interview

For more detailed information, EATN spoke with Dr. Rudolf Kunze who is director of an immunological research laboratory in Berlin, Germany. In 1981, Dr. Rudolf Kunze was a founding member of the AIDS Working Group at the Federal

Health Office, Berlin, of which he was a member until 1989.

# Treatment News update

**EATN:** What is enzyme therapy?

**Dr. Kunze:** In Germany, enzyme preparations (produced by the company Mucos) are available since 1965. The original drug Wobenzym, now available in a modified composition, contained rutoside (a flavonoid) and a mixture of vegetal and animal enzymes (trypsin, chymotrypsin, pancreatin, omegain, papain, amylase, lipase). The action of these enzymes on the organism is mediated by the immune system. Various clinical trials indicate that rutoside acts as a radical scavenger and can "catch" free radicals which result from inflammation (cf. Keith Alcorn, EATN Vol. 3., Nr. 1., p. 8; St. D.).

**EATN:** Are there clinical trials with enzymes in HIV infection?

**Dr. Kunze:** In 1990, results were published from a study by Dr. Hans Jäger from Munich, Germany. In the USA, Wobenzym received the status of a treatment IND (Investigational New Drug) for HIV infection. A clinical trial has just been finished in New York. This trial included patients with advanced HIV disease and was conducted by Dr. Lange in cooperation with PWA/NY. A final report on this study will be available soon. Preliminary laboratory data indicate that enzyme therapy initially leads to an increase in viral load which is followed by a decrease. A possible explanation for this surprising finding could be that enzymes initially mobilize viral antigen from tissues.

**EATN:** Why are currently no clinical trials run on enzyme therapy in Europe?

**Dr. Kunze:** I can only answer from a personal point of view. In 1990 or 1991, an outpatient study was planned at Berlin. At a first meeting, the head physician of a large AIDS hospital was present and denied that

macromolecules like enzymes can be absorbed after oral administration. On the other hand, the ethical commission argued that patient compliance in this trial could not be guaranteed and therefore turned the study down. A double-blind clinical trial is nearly impossible since enzymes are available in pharmacies as OTC drug (without prescription).

**EATN:** But the pharmaceutical company was willing to run a trial?

**Dr. Kunze:** In general, yes. Physicians and healers who had used enzyme products had informed the company that this treatment seemed to be quite successful in HIV patients.

**EATN:** Observations from daily practice indicated that there might be some efficacy?

**Dr. Kunze:** Well, I am a biologist, but as far as I can say from discussions with physicians, yes. In addition to these observations, there are links between autoimmune phenomena in HIV infection and a possible enzyme therapy exist. Enzymes are used for the treatment of various autoimmune diseases. Also, autoimmune phenomena like thrombocytopenia and/or high levels in immune complexes are frequently observed in HIV infection. Based on these parallel observations, the efficacy of enzyme therapy in HIV infection should be checked.

**EATN:** Do hydrolytic enzymes eliminate circulating immune complexes (CIC's) and autoimmune complexes?

**Dr. Kunze:** Yes, and in addition to this mechanism, enzymes may

act on sessile complexes (antigen-antibody complexes in the tissue which are responsible for many problems, including joint pain, kidney dysfunction etc; St. D.).

**EATN:** In which stage of HIV infection should an enzyme therapy start?

**Dr. Kunze:** From a theoretical point of view, I would say as early as possible. We know from clinical trials that even asymptomatic HIV-infected persons in a very early stage of infection already show immunopathological findings in laboratory tests. These data suggest an early intervention with immunomodulating substances. On the other hand, we cannot expect any direct antiviral action of enzymes. We may influence pathological changes in the immune system and we can decrease some immunological reactions (e.g. inflammatory reactions). Today, it is possible to monitor these processes by laboratory tests.

**EATN:** What laboratory tests can be performed in daily clinical practice? Are there surrogate markers for enzyme therapy?

**Dr. Kunze:** All these laboratory parameters are already well-known: soluble interleukin-II receptor (as indicator of T cell activation), beta-2 microglobulin (indicator for T cell proliferation), neopterin (indicator for interaction between macrophages and T lymphocytes), lymphocyte phenotyping (CD4/CD8), and immunoglobulins, especially IgA. In addition, also C-reactive protein (CRP) can be used as a marker for inflammation.

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**EATN:** During what could changes of these parameters be expected, and how often should these laboratory tests be taken?

**Dr. Kunze:** Tests should be taken according to the clinical condition. In asymptomatic HIV-infected persons every six months, in progressive stages more frequently. Today, it is

## Delavirdin (U-90152)

Delavirdin is a new compound that has been developed by Upjohn. Delavirdin is a so-called BHAP drug which are TIBO-like drugs that inhibit reverse transcriptase enzymes of HIV by a different mechanism than the nucleoside analogues. Delavirdin

90152) with protease inhibitor U-75875 or interferon alpha. *Journal of Infectious Diseases* 1995; 171; 61-67

(Note: When I asked C. Peter Mertgen, Upjohn Germany, Medical Sciences Liaison Manager, for new information on U-90152 at the Berlin conference on infectious diseases at March 17 1995, he gave me the xerox copy of an article published in May 1993, and remarked that no updated information is available. Let's hope that Upjohn will improve its information policy soon! St. D.)

## Please answer

The return of the reader's questionnaire attached in the two recent issues of EATN has thus far been very unsatisfactory.

Questions arising from this low response rate range from „do more than a handful of people actually read the newsletter in a time related to publication?“ to „is the questionnaire asking the correct questions?“.

The completion of the questionnaire will help the editorial team to accustom the contents of EATN to their customers needs. Please write to us if you need an additional copy of the form.

possible to monitor an immunopathological process in vitro (in the laboratory; St. D.). In consequence, it is also possible to evaluate substances or certain drugs that act on these immunopathological processes. We did so with enzymes and we found that activating processes in the immune system can be regulated down. These processes include a variety of mechanisms. Based on these findings, the use of enzymes in inflammations in chronic autoimmune diseases has a rational explanation.

has now been tested in laboratory studies in combination either with Upjohn's protease inhibitor U-75875, or with interferon alpha. The results are promising and were published recently. The authors (from Upjohn Laboratories, Kalamazoo, Michigan, USA) write that synergy data from their studies support the potential use of delavirdin with either a protease inhibitor or interferon alpha in patients with AIDS. The efficacy should be evaluated in clinical trials, the authors conclude.

Pagans, P. J.; Chong, K. T.: in vitro inhibition of HIV type 1 by a combination of delavirdin (U-

## Complementary therapies

Sport, or rather physical exercise and activity, can influence the immune system. Therapeutic sport is already part of cancer treatment, and first experiences with therapeutic sport for persons with HIV/AIDS have been published. Yvette Florijn, physical training instructor, from the WIAD (Scientific Institute of German Physicians) has organized a therapeutic sport program for people with HIV at Cologne, Germany. She is now working on a European project which aims at implementing sport programs in other countries of the European community.

## Interview

**EATN:** What is the difference between sport and physical exercise or physical activity?

**Yvette Florijn:** Sport is associated with competition and athletics. Physical exercise is rather well adjusted to individual needs and may also be adapted to certain physical impairments. With regard to what I practiced with a group of HIV-infected people, I would prefer to speak of therapeutic sport. It is somehow similar to physical exercise.

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**EATN:** Is physical exercise a therapy?

**Yvette Florijn:** Therapeutic sport should have some benefit for those who practice it. This benefit concerns physical aspects as well as psychological aspects. If you practice for example long-distance running for half an hour a day, you improve your general condition and perhaps the strength of your muscles. But you also feel better psychologically. This psychological effect is very important and improves the general quality of life. In my opinion, therapeutic sport which is aiming at a functional improvement only (e.g., remedial gymnastics), gets boring after a certain time. Therapeutic sport includes group dynamics, physical exercise combined with pleasure, and a lot more. Function-oriented exercises are just one part of it.

**EATN:** Are certain forms of sport especially recommended to HIV-infected persons, and on the other hand, what are dangerous forms?

**Yvette Florijn:** Some forms are certainly not to be recommended for HIV-infected persons. These include all athletic or competitive disciplines which have an immunosuppressive effect. Combat disciplines (e.g., boxing) should be avoided because of the possible risk of infection. It is generally said, that endurance-improving sport strengthens the immune system. The problem is, that not everybody likes this form of sport. Some people, especially gay men, prefer to go to a bodybuilding studio and have a good feeling after they practiced their exercises. And other persons enjoy the communicative aspect of sport, practiced in a group.

**EATN:** In which stages of infection may HIV-infected people practice sport?

**Yvette Florijn:** In our study

group, we had participants in all stages of HIV infection and AIDS - from newly infected persons to people with full-blown AIDS. The majority of participants remained active in the group until a very late stage of their disease. For some of them, physical capacity became a limiting factor. But they managed to adjust the exercises to their individual condition.

**EATN:** Is it possible to document the positive effects of therapeutic sport by measurements or laboratory data?

**Yvette Florijn:** We evaluated immunological, psychological, and physiological parameters. The physiological condition (cardiovascular capacity) measured after 7 months improved, provided that the person participated regularly in the sport program. Participants of the sport group showed better coping strategies and less anxiety, as compared to an inactive control group. They also felt better generally. As it comes to immunological features, I would be very, very careful. Despite standardization, these parameters are difficult to measure, and they could be influenced by many factors other than therapeutic sport (e.g., pharmaceutical substances, complementary therapies, general condition). I may certainly say that therapeutic sport is not harmful.

**EATN:** Is it realistic to expect an immunological improvement from therapeutic sport?

**Yvette Florijn:** I would be cautious again. You can certainly improve your physical capacity through therapeutic sport. It is

unclear what the immunological effects are. In general, participants from my group showed no decline in laboratory values for 6-12 months. But the question is: Wouldn't these persons have remained stable as well, even without therapeutic sport? Sport is not a remedy for all ills.

**EATN:** Could you please tell us something about your European project?

**Yvette Florijn:** This project, sponsored by the EU, aims at passing on our experience to other European countries. For the time being, we cooperate with the Netherlands and Italy. We try to find out: What are the possibilities, and what are the difficulties in implementing a therapeutic sport program. By the end of 1995, a manual will be published in four languages which summarizes our experiences and gives a practical orientation for those who wish to establish such a program.

**EATN:** What are the costs of a therapeutic sport program?

**Yvette Florijn:** The most expensive factor is the therapist (about 30 ECU/hour in Germany). In most countries, the gymnasiums are owned by the state and their use is free of charge. Sometimes, equipment has to be bought.

**For further information, a recent (German-language) publication by the WIAD is available through bookstores: Handbuch "Sport und HIV-Infektion". Baden-Baden: Nomos Publ. 1995. If you want to know more on the European project, please contact Yvette Florijn, Wissenschaftliches**

# Treatment News update

Institut der Ärzte  
Deutschlands e.V.,  
Godesberger Allee 54, D-53175  
Bonn.

## Countries

### Belgium

The AIDS service organization Infor sida has started an action in order to improve the dialogue between the general practitioner and HIV-infected patients. In cooperation with Soci,t, Scientifique de Médecine Générale (S.S.M.G.), Infor sida organizes comedy/theatre performances which demonstrate the reality of seropositive patients in general practice. As part of the action, a brochure "Histoires d'en parler" has been published which is available through Infor sida, rue de Haerne 42, B-1040 Bruxelles.

### France

ARCAT-Sida has released a draft version of a Community Vaccine Network Working paper. This document is supposed to set down the minimum conditions demanded by the community before phase III clinical trials of anti-HIV vaccines begin. The 80 pages-paper is available from ARCAT-Sida, Marie Ahouanto, 13 Boulevard de Rochechouart, F 75009 Paris. Comments and suggestions should be forwarded to Marie Ahouanto as soon as possible.

In January 1995, ARCAT-Sida has published the third edition of the AIDS and HIV Treatment Directory France. The previous,

second edition of the Treatment Directory France was published in December 1993. A database with information including trials which were completed in 1994, supplied by the sponsors, is available since last year. This database forms the basis for the current printed edition of the treatment directory. The complete French version (VIH et SIDA: Répertoire des essais thérapeutiques en France, 3<sup>ème</sup> édition) includes about 100 trials, the English edition some 60 clinical trials. Both volumes are available for 100 FF (+ 36,50 FF shipping cost) from ARCAT-SIDA, 13, boulevard Rochechouart, F 75009 Paris. Tel.: (+33-1) 49 70 85 90 Fax: (+33-1) 49 70 85 99.

### Germany

An update of the German AIDS Treatment Directory has been published and is available from AIDS-Zentrum, Robert-Koch-Institut, Reichpietschufer 74-76, D-10785 Berlin. A new edition of the European AIDS Treatment Directory becomes more and more unlikely. At a meeting at Paris, the institutions and organizations involved at producing the first edition (which was published in 1994) agreed that it will be to difficult to collect sufficient data from all European countries. Organizations like National AIDS Manual (NAM) and Arcat-Sida, working on a national level in France or in the U.K., respectively, will continue to exchange information on ongoing clinical trials.

### Switzerland

## New AIDS Treatment Information Handbook Published

In cooperation with several drug companies, P.W.A. Switzerland has published a loose-leaf book on AIDS therapies. The some 80-pages book contains chapters on basic knowledge on HIV, symptoms and treatment for HIV-related diseases (opportunistic infections, neurological complications, tumors, and other), a special section on antiretroviral drugs, another one on complementary therapies, and a large service section which provides addresses around Switzerland. It is planned to update the handbook at least once a year. The handbook is available in German and French. People with HIV may obtain a complimentary copy free of charge. For further information, please contact:

Aids Info Docu Schweiz  
P.O. Box  
Schauplatzgasse 26  
CH - 3001 Bern

### Changes in Drug Policy

On Tuesday, February 14 1995, Europe's biggest open-air drug market Letten, located in the city of Zürich, was closed down. While clearing the place, a former train station, from drug users and dealers, 300 policemen were observed by 21 television teams and numerous journalists. Only three years ago, Zürich had trouble with another well-known place for drug trade, the "Platzspitz" which was closed down in 1992. The close-down of the Letten signals a change in Swiss drug policy. Drug users who lived in Zürich will be driven back to their home communities, and the so-called "scene" will be decentralized. As the Swiss journal AIDS Infothek (February 1995) reports, this decentralization could impair AIDS prevention in drug users. In many small cities and villages, sterile syringes and clean needles are not yet available. According

to an article in the German newspaper Frankfurter Allgemeine Zeitung (February 15 1995), the program for a controlled distribution of drugs (including heroin) will be expanded. At Zürich, the number of places on the program will increase from presently 100 to 300. Whether this program will be a real help in the fight against drug use, remains a controversial question. With some estimated 30.000 drug users, Switzerland has one of the largest drug scenes in central Europe.

## United States

### New AIDS Information Service Available

On October 31 1994, the new HIV/AIDS treatment information service (ATIS) opened in the US. ATIS provides information on currently approved HIV/AIDS therapies in the US and is operated by the CDC National AIDS Clearinghouse. ATIS is staffed by health care professionals who use the National Library of Medicine database of HIV/AIDS treatment guidelines. Spanish-speaking reference specialists are available and a TDD line for the deaf is offered. The telephone number is: ++1-800-448-0440. Fax: ++1-301-738-6616. Mailing address: P.O. Box 6303, Rockville, MD 20849-6303.

Source: CDC HIV/AIDS Prevention Vol. 5, No. 3, Winter 1994/95, p. 3

## Drug Companies

### Wellcome, Once More

After initial resistance against Glaxo's 9 billion pound bid, Wellcome's board now seems to have resigned in favor of the offer. At the International Conference on combination therapies, held March

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25-26 at Berlin and sponsored by Wellcome, rumours went that the take-over contract has already been signed. Therefore, it becomes more and more likely that Glaxo will take over Wellcome. Strategies for an effective development of new antiretroviral substances should play an important role for a pharmaceutical company that may be expected to become world's biggest drug company. Successful programs like "Foundation Wellcome" should be continued and extended in the future. A close cooperation with the community could help to implement successful strategies in the future.

### Unclear Strategy by Upjohn

Medroxyprogesterone acetate (MPA) is a hormonal substance that is in use since several years for the treatment of hormone-dependent breast cancer and other gynecological tumors. MPA also stimulates appetite and weight gain and has therefore been used in the treatment of HIV-related weight loss and cachexia. At the 3rd German Conference on Infectious Diseases, held from March 15-18 1995 at Berlin, Upjohn company presented preliminary results from a clinical trial with MPA conducted by Daniele Scevola, Professor at the Institute of Infectious Diseases, University of Pavia, Italy. These results indicate that there might be some beneficial effect of MPA in the treatment of AIDS patients who show an increase in weight and body mass index (BMI), as compared to a control group which received placebo.

The presentation of data at a press

conference held at March 17 1995 at Berlin, was not convincing. Precise information on initial weight (in kg or pounds), stage of disease of the patients enrolled or survival time was not available. It was said that quality of life was better for patients who received MPA - but quality of life was not measured by psychological tests. MPA is not approved for the treatment of HIV-related weight loss, cachexia or wasting syndrome. Upjohn's strategy in further development of the drug for these indications is confusing. A clinical phase III trial with 120 patients has started in May 1994 at Lyon, France (cf. AIDS and HIV Treatment Directory France 1995, p. 78). It is unclear whether this trial aims at approval of MPA for treatment of HIV-related weight loss. At the Berlin press conference, representatives from Upjohn company argued that MPA will be available for example in Germany even without approval for this indication since physicians have the freedom to prescribe whatever they think to be an appropriate therapy.

The approval of a drug includes the evaluation of data by state and governmental offices. So-called off-label use of drugs which are approved for certain diseases, but not necessarily for the treatment of HIV infection is common. Some 90% of AIDS patients in the United States receive off-label drugs. The problem is that health insurances not always cover the cost for these drugs. If sufficient data on MPA exist, why doesn't Upjohn proceed towards the application for approval?

# EATN special

## Taking an answer for good news

### Hoffmann-La Roche responds to EATN

by Matthias Wienold, Hannover

In EATN Vol. 3 No.3 we published a news item with regard to Hoffmann-La Roche not answering the questions of ACT UP Paris referring to their Invirase (Saquinavir) trials programme in Europe.

Serious doubts had arisen to the aims and goals of this large clinical trials programme and proposals had been made, how to adequately adjust the design of the trials to the communities needs and demands.

The major concerns were:

- 1) the programme is mainly based on the aim of marketing the compound rather than trying to answer the most imminent questions
- 2) interim results of the trial will also be used to market the ddC/AZT combination therapy in Europe
- 3) the number of participants in individual centres is too low for experience with the drug to be developed
- 4) neither the drop in CD4 cells by percentage nor by absolute numbers are respected as endpoints in the trial
- 5) Hoffmann-La Roche does not adequately respect the demands brought to them

The resulting exchange of letters between EATN and Hoffmann-La Roche is tedious to document (and would need to be translated from German). In publishing the

statement by Hoffmann-La Roche I do hope to enliven the discussion about a systematic and well structured co-operation between community AIDS treatment activists and the pharmaceutical industry in Europe in general.

When I first read the statement I was disappointed at how little commitment and strategic perspective the company seemed to have developed. Dr. Kramer, the communications manager AIDS at Hoffmann-La Roche Basel, however, assures me in a letter dated 21 March 1995 that the companies commitment to continue and continually improve co-operation with all community groups including the treatment activists is existant. EATG is involved in this process.

Overall, my conclusion is that Hoffmann-La Roche in Basel is gradually developing a proactive programme that is more profiled and coherent in both marketing and developing drugs and displays a corporate identity. The merger of Glaxo and Wellcome might just as well be a reason for this as the mounting pressure from the community. The company demands reliable and stable partners in this process. EATG is currently discussing a proposal for European Community Advisory Boards in clinical research (available in English through the EATG secretariate, address on back page). Such a board has the potential of becoming a stable and reliable independant partner.

## The Study design of the Saquinavir international phase III clinical programme

(official statement by Hoffmann-La Roche, 17 February 1995)

### The development of a medicine proceeds according to rules defined by the scientific community

Because AIDS is a major public health issue, the responsibility for therapeutic research in this field is naturally shared between the various groups involved: government monitoring and research agencies, doctors and patient associations. A programme on this scale cannot be planned and implemented without their input and agreement. Numerous international experts have taken part in discussions about this trial, including a number of AIDS patient organizations in America and Europe.

Our role is to implement the measures required to demonstrate efficacy as demanded by the representatives of all interested parties. This approach should be based on methods that are scientifically reliable, ethically controlled, rigorously applied and constantly monitored throughout the trial. We owe it to the patients to apply this degree of rigour. It constitutes the ethical basis of clinical research and is enshrined in the public health code.

### The development of saquinavir is a case in point

This trial is part of a complex clinical development programme and follows a series of 4 phase II clinical trials (three European

studies conducted in France, the UK and Italy and one in the USA). The results of the first three studies were published during the Berlin Congress in 1993, while those of the American study, ACTG 229, were announced in Yokohama in August 1994. Each of these trials has provided answers to one or more specific questions concerning the antiviral activity and safety of this product. In phase II more than 380 patients have been tested with varying dosages of saquinavir. Saquinavir in combination with AZT has been compared with AZT monotherapy, and a triple combination (AZT/ddC/SQV) has been compared with the double combinations (AZT/ddC, AZT/SQV).

Thus, biological activity is already well known. It has been assessed on the following criteria: CD4 lymphocyte count, viral quantification over periods of around six months. Saquinavir has been very well tolerated in these trials.

### **The need for clinical efficacy**

The key therapeutic question in the saquinavir protocol cited by way of illustration is no different from that posed by other phase III trials in this field: does the degree of biological activity shown in the phase II trials translate into improved clinical efficiency over currently available treatments?

Since so many uncertainties currently surround the predictive value of the latest virological markers, the scientific community cannot yet definitively validate this approach.

However, the future is not static. Knowledge is developing rapidly, and the rules and points of reference are changing. This trial may have to be adapted to new requirements, and Roche has

# **EATN special**

appointed a committee of expert clinicians to advise accordingly.

The methods used in these trials should first and foremost enable us to demonstrate clinical efficacy and assess the tolerability and safety of saquinavir when administered in combination to a sizable number of patients for longer treatment periods than those used in previous phase II trials.

A considerable amount of effort is being invested in this endeavor. Such a commitment is justified only by the certainty of obtaining interpretable results that will answer the specific question posed. The methods used in this trial will enable us to achieve this important objective.

### **A trial without precedent, a combined and continually evolving approach**

This trial is without precedent in clinical research on antiretroviral agents. It is the first time that the clinical effects of an HIV protease inhibitor, when administered in a triple or a double combination as first-line treatments, have been evaluated in patients.

- The symptomatic and asymptomatic patients involved in this trial have received short-term (less than four months) or no treatment with AZT prior to the trial and have CD4 lymphocyte counts between 50 and 350.

- Four therapeutic

regimens are compared, including two double combinations and one triple combination (AZT/ddC/saquinavir, AZT/saquinavir).

- These three regimens are compared with the current standard first-line treatment: AZT as monotherapy and AZT/ddC.

In addition to the therapeutic innovations cited above, considerable resources are also being devoted to evaluating the therapeutic benefit.

- The clinical evaluation is being complemented by advanced virological techniques including the investigation of plasma RNA viral load by quantitative PCR, investigation of the sensitivity of the virus to the various antiviral agents used and a phenotypic type (SI/NSI).

- The patient's quality of life and the impact of the treatment on patient care are also assessed in parallel.

The development of this protocol has enabled us to incorporate the results of the latest phase II saquinavir studies. As a result, significant modifications were made to the experimental design of the trial during the first half of 1994.

The trial was initiated on an international scale in August 1994 and it will include 3'300 patients in 150 centers in 21 countries. About 1000 patients are currently (end of January

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1995) being treated in this trial.

## **A closely monitored trial**

A trial monitoring committee (DSMB) that is independent of Roche has already been appointed. It is composed of three clinicians, an ethicist and a statistician and regularly reviews the entire programme. Its mandate is to advise on ethical issues, safety and efficacy data. Thus, the DSMB also safeguards the patients interests. It will have to assess to the latest scientific results relevant of the trial and will inform Roche if it considers that the trial needs to be modified or terminated.

An international steering committee, composed of investigators from various countries and Roche representatives, is responsible for monitoring the progress of the trial internationally and will suggest and implement any necessary changes to the protocol.

It should be stressed that this protocol reflects the latest available findings on saquinavir. Because the field is developing rapidly, will ensure that the protocol takes into account relevant new scientific findings.

## **A prolonged trial period for patients receiving little or no previous treatment**

The DSMB will decide upon termination of the trial when the number of clinical events occurring within the trial allow

conclusions to be drawn on the clinical efficacy of saquinavir. Depending on the progress made, the trial could be terminated from the 30th month onward, or earlier (each patient is treated for approx. 18 months, to which should be added the enrollment period of 12 to 15 months for the 3'300 patients).

## **Progress criteria for laboratory parameters**

Given the current uncertainties about the criteria for assessing the progress of the illness by laboratory parameters, the provisions of the protocol allow individual patient benefit to be taken into account. The investigator will be able to freely interpret laboratory changes within the context of the patient-doctor dialogue. However biological end-points cannot at this stage substitute for a primary end-point defined as an AIDS defining event.

## **Unblinding**

Unblinding as a result of changes or deterioration in laboratory markers or at the request of the doctor involves significant methodological risks.

Premature unblinding may lead to a potential bias in favour of one particular therapeutic regimen, regardless of whether the patients remain in their randomization arm or are transferred to the roll-over protocol. Changes in therapy following the initial randomization will make efficacy comparisons of between the different treatment arms more

difficult.

For a given investigator or centre, knowledge of the treatment received by patients who have, for one reason or another, withdrawn from the trial, might affect, consciously or unconsciously and in varying degrees, the objectivity of the clinician in implementing the trial protocol.

## **Flexible follow-up procedures adapted to the needs of the protocol**

The tier 1 and 2 procedures will efficiently reduce the workload for the overall trial without diminishing the quality of care provided to the patients. This original approach greatly reduces administrative workload of collecting data from the tier 2 centres. These procedures have been introduced to facilitate trial management, thus allowing a degree of flexibility in the management of patients.

In fact, this flexible arrangement should promote protocol compliance.

In any case, each clinician may prescribe whatever laboratory tests he deems necessary for the follow-up of individual patients. Doctors retain the responsibility for the medical follow-up of their patients, which will be identical in all centers since patients are seen with the same frequency.

## **Development of a medicine and therapeutic strategy**

Within the present scientific context, the trial in question is a key element in gaining an understanding of this new drug, and involves the use of the latest therapeutic combination regimens and new methods for evaluating antiretroviral activity.

The protocol does not envisage

the evaluation of a succession of therapeutic regimens in terms of strategy. The evaluation and success of this trial concerns not only Roche but also other pharmaceutical companies involved as well as public health authorities and independent research organizations.

For its part, Roche is actively working within the ICC (cooperative venture between pharmaceutical companies involved in AIDS research) to implement trials designed to evaluate therapeutic combination regimens.

Finally, Roche is undertaking efforts to make saquinavir further

# EATN special

available under conditions yet to be specified before it is officially registered. There is an urgent need for the rapid development of new treatments and improved therapeutic strategies.

While the general debate on the utility and design of phase III trials has been under way for some time now, there is not yet sufficient information on biological end-points to justify

abandoning clinical end-point studies. As the debate continues these current uncertainties should not prevent us from actively pursuing our attempts to develop appropriate and essential treatments.

Within this overall framework, dialogue with community based organizations is essential and should continue in future.

## being active in Switzerland

Bernhard Bürki is a member of EATG since 1994. He continues the representation of the Swiss AIDS service organisations and the PWA treatment activists that began in 1991.

Bernhard is 44 years old. He is the father of four and used to be a teacher for nine years. After completion of his medical training he worked in the regional hospitals of Interlaken and Thun, Switzerland. Later he also became deputy director of the AIDS coordination unit of the Kanton Bern in his capacity as an internal medicine specialist and was head of the clinical counselling services for AIDS in that region. He has lately become the leader of an HIV prevention programme in the women's prison of Hindelbank and covers the area of AIDS therapies as a consultant to the Swiss AIDS-Hilfe and PWA Switzerland.

In addition to these activities Bernhard is involved in publications around insurance

issues and teaches at a college for nursing. He has discontinued his activities at a local radio station.

With regard to AIDS his topics of special interest are prevention and therapy. His involvement in issues around AIDS came about rather accidentally. „I was looking for a new medical challenge.“

Meanwhile Bernhard Bürki is glad that he decided to work in the AIDS-field. „HIV-infection and AIDS are not only limited to medicine or medicosocial problems. There are a lot of additional aspects, e.g. legal, ethical, religious issues, and with regard to the interconnectiveness of medicine and public politics - the connection is nowhere closer than in HIV and AIDS.“

### AIDS in Switzerland

cummulative AIDS cases	4,105
rate per million inhabitants	586
cases recorded	
in 1992	646
in 1993	679
expected in 1994	739
rise 1994 over 1993	8.8%

(source: European Centre for the Epidemiological Monitoring of AIDS)

Homo- and bisexual and intravenous drug-users account for one third of the cases each. Approximately one fifth of cases is attributed to heterosexual transmission of HIV.