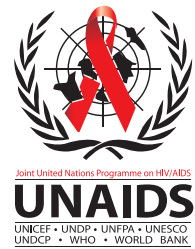




HIV-NAT

The HIV Netherlands Australia Thailand
Research Collaboration

*A model for HIV-AIDS clinical
research in a developing country*



UNAIDS BEST PRACTICE COLLECTION

Acknowledgement

This report has been written by Eugène D.M.B. Kroon, M.D., with support from Chaiwat Ungsedhapand, M.D., Chris Duncombe, M.D., Mena Chuenyam, R.N., and Professor Praphan Phanuphak M.D., Ph.D.

HIV - NAT

The Netherlands Australia Thailand Research Collaboration
Bangkok, Thailand.

UNAIDS/00.19E (English original, July 2000)

Joint United Nations Programme on HIV/AIDS (UNAIDS) 2000. All right reserved. This document, which is not a formal publication of UNAIDS, may be freely reviewed, quoted, reproduced or translated, in part or in full, provided the source is acknowledged. The document may not be sold or used in conjunction with commercial purposes without prior written approval from UNAIDS (Contact: UNAIDS Information Centre).

The designations employed and the presentation of the material in this work do not imply the expression of any opinion whatsoever on the part of UNAIDS concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers and boundaries.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by UNAIDS in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

UNAIDS – 20 avenue Appia - 1211 Geneva 27 - Switzerland
Tel.: (+41 22) 791 46 51 - Fax : (+41 22) 791 41 65
e-mail: unaids@unaids.org - <http://www.unaids.org>

UNAIDS BEST PRACTICE COLLECTION

HIV-NAT

The HIV Netherlands Australia Thailand Research Collaboration
Thai Red Cross AIDS Research Centre

*A model for HIV-AIDS clinical research
in a developing country*



Joint United Nations Programme on HIV/AIDS

UNAIDS

UNICEF • UNDP • UNFPA • UNESCO
UNDCP • WHO • WORLD BANK

UNAIDS

Geneva, Switzerland
2000

Table of Contents

Message from Chairman	2
Foreword	3
Goals	7
Primary goal	7
Secondary goals	8
History	9
Overview	10
Foundations and resources	10
Establishment	11
Needs	12
Expansion	14
Information dissemination	15
Transparency	15
Ongoing funding	15
Further training and development	16
Internal review	16
Advisory board	17
Issues encountered	18
Guidelines	18
Long-term treatment	19
Sponsor commitment	20
Partnerships and alliances	21
Founders	21
MOPH	21
Patient organizations	22
Sponsors	22
Monitoring and evaluation	24
The future	25
Lessons learned	27
References	30
Appendix A: Clinical Trials	31
Appendix B: Organisation Structure	33
Appendix C: Case Interviews	34

Message from Chairman

As Secretary General of The Thai Red Cross Society, it is my great pleasure to be associated with HIV-NAT.

HIV-NAT was conceived in 1995 with the vision of three physicians dedicated to the fight against HIV/AIDS. Together, Professor Praphan Phanuphak, Professor Joep Lange and Professor David Cooper have steered HIV-NAT from its small beginnings to an internationally recognized research organization.

The new HIV-NAT building, donated by The Thai Red Cross Society, provides much-needed space for the expanding research centre. With the generous support of unrestricted grants from F. Hoffman La Roche “Blue Sky” initiative and Bristol-Myers Squibb, the new facility is equipped to provide a comfortable working environment for its staff, as well as state-of-the-art communication and computer technology.

The Thai Red Cross Society will continue to support HIV-NAT and its commitments to conduct research in Thailand to international standards and to provide access to treatments for Thai people living with HIV/AIDS.



Mr. Phan Wannamethee
Chairman, HIV-NAT International Advisory Board,
Secretary General, The Thai Red Cross Society

Foreword

In 1984, the first known Thai HIV infected patient returned to Thailand from the United States to be treated in Bangkok's Ramathibodi Hospital. One year later, the first two patients were diagnosed with HIV related illnesses in Thailand by Professor Praphan Phanuphak, now one of the Co-Directors of HIV-NAT. One of these patients, all men who had had sex with men, had never lived outside of Thailand. In 1987, an HIV epidemic became apparent among injecting drug users in Bangkok. Soon afterwards, a rapid spread of HIV was observed in Thai commercial sex workers and their clients, first in the northern provinces only but soon afterwards in other parts of the country. Since the late 1980s, HIV has been endemic in Thailand, with heterosexual contact being the predominant mode of transmission. The initial epidemic with HIV subtype B in men having sex with men and injecting drug users may have been quite distinct from the early epidemic with HIV subtype E in female sex workers and their clients. Currently, subtype E is by far the most common HIV subtype encountered in Thailand, regardless of risk behaviour or mode of transmission.

Thailand's impressive and admirable response to the epidemic has made the country a role model in HIV prevention. Since 1992, large-scale prevention campaigns, such as the internationally well-known '100% condom program'¹, have led to a steady decline in the rate of new infections. Nevertheless, an estimated 1.0 million people, or 1.9% of the population, are now living with HIV in Thailand, a country with a total population of just over 60 million.² In addition, an estimated 20,000 children are born yearly to HIV-infected mothers and 19% to 25% of these children would become HIV-positive around the time of delivery without any interventions.^{3,4} Currently, the official cumulative number of AIDS cases (people with HIV related illnesses) stands at 117,000.⁵

Thailand is usually regarded as an intermediate developed country after 30 years of more than 4% growth of per capita GDP per year and with 13% of the population living below the official World Bank poverty line in 1997. However, the recently acquired wealth is unevenly distributed with the richest 10% of the population earning 21 times the

amount earned by the poorest 10%. Some 23 million people are not covered by any kind of basic health insurance, while 85% of all workers, the poor and unemployed are not covered by any of the existing social security networks.^{6,7,8}

When therapy with two nucleoside reverse transcriptase inhibitors (NRTIs) became the standard of care in the developed world in the mid 1990s, it was calculated that implementing this standard of care in Thailand for all eligible HIV infected individuals would have cost 6.3 times the entire budget available to the Thai government at the time for HIV/AIDS prevention, counselling, testing and treatment.⁹ With the introduction of highly active antiretroviral therapy (HAART), consisting of at least three antiretroviral drugs taken together, as the standard of care for HIV infection in developed countries, what is now considered optimal treatment is completely out of reach of most HIV infected individuals in Thailand.

More affordable and effective treatments, either new compounds or existing compounds put to use in innovative ways, are much needed in Thailand and other heavily affected countries with limited resources. However, treatment innovation is also crucial to developed nations, as the number of available drugs is still limited, while drug resistance to existing compounds is an increasing problem. The side effects and the complexity of the available treatments make adherence to these treatments difficult for some patients and the toxicities of available compounds can be severe in some individuals. To prove that new compounds or new approaches in HIV treatment, or in the prevention of HIV transmission, are indeed safe and effective, safety and dose finding studies with such compounds need to be conducted (phase I and II studies). Subsequently, randomized efficacy studies in larger populations (phase III studies) must take place.¹⁰ Due to the wide availability of HAART in the developed world and the relatively small HIV-infected population in these countries, enrolment of sufficient, motivated, HIV-infected participants in research projects is difficult. It would seem logical to move clinical HIV research efforts to developing countries, where more than 95% of people infected with HIV live.

Another compelling reason for moving clinical HIV research efforts to developing countries can be found in the properties of many

antiretroviral compounds which make them more likely to be sensitive to ethnic factors, according to the definitions of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as stated in the guideline *Ethnic Factors in the Acceptability of Foreign Clinical Data*.¹¹ Such properties include, for example, a narrow therapeutic dose range, a single metabolic pathway, a high inter-subject variation in bio-availability, and high protein binding. For practical purposes, the ICH guideline distinguishes world-wide three large ethnic groups: Asians, Blacks and Caucasians. While the majority of participants in clinical HIV research in the developed world have been and are Caucasians, the countries currently most affected by the HIV epidemic are inhabited by predominantly Black and Asian populations.

Finally, the majority of children born to HIV-infected mothers, and therefore at risk of HIV-exposure and transmission, are born outside of the developed world.

HIV clinical research is mostly sponsored by large, international pharmaceutical companies, but also by international humanitarian organizations and government bodies. Despite good reasons for expanding HIV clinical research efforts and for moving research efforts to developing countries, sponsors seem reluctant to conduct research there.

One of the major reasons for this reluctance seems to be a widespread concern on the part of the sponsors as to whether local investigators, ethics committees and the overall infrastructure in developing countries can meet internationally accepted standards of clinical research conduct. Currently, the most widely accepted standard for conducting research involving human subjects is the so-called *Guideline for Good Clinical Practice* as formulated by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH GCP).¹² Adherence to this standard is actually mandated by law in many countries and ICH GCP provides an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Demanding compliance with this standard aims to provide public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in

the Declaration of Helsinki, and that the clinical trial data are credible. The ICH GCP standard defines the role and obligations of the ethics committee, the investigator and the sponsor involved in clinical research. ICH GCP also dictates how the study protocol and the written information for potential research participants should be structured.

Thai legislation currently does not demand that clinical trials be conducted according to the ICH GCP standard. Nevertheless, the majority of potential trial sponsors will only support clinical research when they believe that conduct according to this standard can largely be guaranteed. Often, this is because of obvious managerial, scientific and ethical concerns on the part of these sponsors, but sometimes also because sponsors want to use the clinical research data for submission to regulatory authorities in countries where ICH GCP conduct is mandatory. The ultimate aim of any clinical research study should be its publication in a peer reviewed medical journal, most of which will only accept data gathered according to Good Clinical Practice standards.

HIV-NAT's *raison d'être* can be found in this paradox; little HIV clinical research taking place where it seems most applicable and needed.

Goals

HIV-NAT is a collaboration between:

- the Dutch National AIDS Therapy Evaluation Centre (NATEC), Department of Internal Medicine, University of Amsterdam, the Netherlands;
- the Australian National Centre in HIV Epidemiology and Clinical Research (NCHECR), University of New South Wales, Sydney, Australia; and
- the Thai Red Cross AIDS Research Centre (TRC-ARC), Bangkok, Thailand.

HIV-NAT's offices are located at the Thai Red Cross Society's premises in Bangkok and administratively, HIV-NAT is one of the four branches of the Thai Red Cross AIDS Research Centre. The research projects conducted or coordinated by HIV-NAT enrol patients in various hospitals throughout Thailand.

Primary goal

NATEC and NCHECR are established HIV clinical research organizations which conduct and coordinate multi-center HIV clinical trials in the Netherlands and Australia.

The primary goal of HIV-NAT is to establish a similar multi-center HIV clinical research organization in Thailand, to conduct and coordinate clinical intervention studies, and, potentially, vaccine studies, according to the ICH GCP standard in Thailand and the region.

The aim of these studies is to yield answers to locally and regionally relevant research questions. So far, this has implied that most research protocols were generated locally by HIV-NAT. Research questions are formulated either within the organization itself or with input from either the Independent International Advisory Board or the AIDS Division of the Thai Ministry of Public Health [MOPH]. HIV-NAT, however, may also participate in studies designed by third parties, as long as participa-

tion in these studies is likely to yield data and results that are valuable in the context of the local HIV/AIDS situation.

By conducting HIV clinical research according to the ICH GCP standard, HIV-NAT aims to convince sponsors that scientifically and ethically sound clinical research can be conducted in Thailand and, ultimately, to invest in such research in Thailand. Conducting the studies will make effective drugs available to study participants, will strengthen the HIV research infrastructure and the HIV care infrastructure in general, and will provide health care workers with valuable experience with newly available treatments.

Secondary goals

Secondary goals of the collaboration are:

1. to conduct basic biomedical research related directly to the clinical trials; and
2. to serve as a training center in the practical, ethical and scientific aspects of HIV care and research for staff from government and university hospitals and related organizations in Thailand and the region.



New HIV-NAT office on Rajdumri Road

History

The Directors of NATEC, NCHECR, and TRC-ARC, Professors Joep M.A. Lange, David A. Cooper and Praphan Phanuphak met frequently at international HIV conferences and meetings. Given the reluctance they perceived on the part of pharmaceutical companies and other sponsors to move HIV related clinical research to areas where HIV is most prevalent, they established the need for a multi-center clinical trials organization in Thailand when they met in November 1995. The three founders formulated the Statutes of the organization and, in July 1996, a Dutch HIV clinical trials physician was stationed in Bangkok to prepare the first two studies together with a newly recruited Thai clinical research nurse. The first study for 75 participants started in September 1996 and in January 1997 the newly formed Independent International Advisory Board, overseeing the research activities, met in Bangkok for the first time.

The first ICH GCP training workshop for potential future study sites in Thailand took place in February 1997. Successful conduct and completion of the first two studies raised the interest of sponsors in HIV-NAT and expansion of research activities led to recruitment of additional staff. In October 1997, the first study results were presented at a peer-reviewed international meeting in Manila. In November 1997, HIV-NAT expanded its activities to its first satellite site. In April 1999, the HIV-NAT staff moved into HIV-NAT's own office and clinic facilities where the first pharmacokinetic studies were recently conducted.

Overview

Foundations and resources

After establishing the need for an HIV clinical trials center in Thailand, the three Directors formulated the goals of the organization in the Statutes and agreed on the responsibilities and tasks of each of the three organizations involved.

Prof. Joep Lange and Prof. David Cooper, directors of established HIV clinical research organizations, lobbied the pharmaceutical industries to raise their interest in moving research efforts to Thailand. Prof. Praphan Phanuphak accessed sources of support within Thailand and raised the interest of the AIDS Division of the MOPH in HIV-NAT. Administratively, HIV-NAT was to be one of the branches of the Thai Red Cross AIDS Research Centre and its offices would be located at the Thai Red Cross Society's premises.

NATEC, NCHECR and TRC-ARC shared the expenses for core infrastructure (office and laboratory supplies) and continue to share the salaries of some staff members and part of the expenses for training of HIV-NAT staff. External study sponsoring (from pharmaceutical companies, the Thai MOPH and the US National Institutes of Health) funds the majority of research staff salaries, research drugs, laboratory assays, additional training for HIV-NAT staff, and funds the presentation of study results at meetings in Thailand and internationally.

To assure external monitoring and guidance, the Directors approached independent experts in the field of HIV with different scientific and professional backgrounds to establish an Independent International Advisory Board of 10 members. The Advisory Board oversees research progress, evaluates research proposals and helps establish policy and research strategy.

NATEC sent an experienced clinical trials physician to Bangkok. NCHECR provided resources to hire a Thai counterpart physician and, later, sent one of its experienced physicians as well. TRC-ARC provided nursing and laboratory support, plus office and clinic space.

NATEC and NCHECR provided statistical and data-management advice and made their existing staff available for consultation on all aspects of conducting clinical research.

HIV-NAT applied for, and received approval from the Thai National AIDS Committee which oversees the national response to the epidemic. Given the key role of the AIDS Division of the MOPH in policy making and implementation of HIV therapy in Thailand, the Directors envisioned an active role for the MOPH in HIV-NAT by having a representative serve on the Advisory Board, providing political and financial support whenever possible, allowing its hospitals to participate in studies if appropriate, facilitating in the import of study drugs, and by considering HIV-NAT study results when formulating national policy.

Establishment

The final impetus for the establishment of HIV-NAT came at a GlaxoWellcome sponsored meeting in Phuket in late 1995. HIV-NAT commenced operations in July 1996 from a single room with one telephone line, one physician, two nurses and two part-time laboratory staff members.

The Directors decided that the first HIV-NAT research project should study the feasibility of dose reduction of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination in Thai patients, as such an approach, if successful, would lead to substantial reduction of treatment expenses. Also, such a study should logistically be relatively simple and, therefore, a suitable first project.

The idea to study lower doses of NRTIs was triggered by the observed lower average bodyweight of Thai HIV positive patients in comparison with the populations in whom NRTIs were originally studied, and by the positive results shown by low dose phase II trials with the NRTI zidovudine (ZDV/AZT).^{13,14,15,16} As anticipated, international headquarters of pharmaceutical companies, while supportive of the research collaboration initiative as such, were reluctant to embark on a first study with HIV-NAT. The local medical director of Roche (Thailand) Ltd. and the AIDS Division of the MOPH were willing to invest in the first randomized low-dose study using the drugs ddC and AZT for 110 participants. Shortly afterwards, the local management of Bristol-Myers Squibb (Thailand) Ltd.

gave their support to a dose finding study with the drugs didanosine (ddl) and stavudine (d4T) in 75 Thai participants and were willing to share the expenses of that study with the AIDS Division of the Thai MOPH.

At establishment, the Dutch physician was joined by a senior Thai Registered Nurse with more than 12 years experience from the USA, and familiar with the basics of ICH GCP. With input from the Directors and statistical staff in Amsterdam and Sydney, the first two protocols were developed. A plan of the locally existing and non-existing infrastructure needed to conduct clinical HIV research was formulated.

Needs

Based on shared experience from NATEC and NCHECR, and with the ICH GCP standard in mind, the following inventory of required resources was made:

- physician-researchers and statisticians to develop a study protocol;
- a physician or nurse-coordinator to submit the protocol to the appropriate ethical and regulatory authorities, to oversee overall study progress and to eventually write the final manuscript in collaboration with a statistician or epidemiologist;
- an ethical committee functioning according to the ICH GCP standard;
- a research pharmacist responsible for packing, labelling, storing, dispensing and accounting for study drugs and for the destruction or return to the sponsor of unused study drugs;
- a statistician or epidemiologist to provide the study randomization program (if applicable to the study), ongoing statistical advice, and a final analysis of the study data, to serve as the basis for the study manuscript;
- physicians and nurses to provide consultations to the study participants and to complete the patient records in the clinic and the study Case Record Forms (CRFs);
- clinical chemistry, haematology, immunology and virology laboratories, all working according to documented standardized methods and participating in internal and external quality control programs;

- a data manager to build study databases, designs CRFs and streamline data collection and checking;
- data-entry staff;
- independent monitors to check the accuracy of data gathered and to check the overall quality of study conduct, including the clinic facilities, laboratories and medication storage; and
- administrative and financial support staff who also calculate study budgets.

HIV-NAT's long-term goal is to have all these resources locally available in Bangkok and to be financially independent through study generated income.

HIV-NAT limited the first two studies to a single site, Chulalongkorn Hospital in Bangkok, in an attempt to establish a 'center of excellence', which could subsequently serve as a teaching model for future participating research sites throughout the country and the region.

Most obstacles encountered in getting the first two studies off the ground and conducted were of a logistical or administrative nature. This means that a few tasks that needed to be performed were not previously performed in the hospital and that people needed to be appointed and trained to complete these tasks. Mostly, it meant that required tasks had already been performed in the institution but had not been standardized or recorded to the extent required by the ICH GCP standard.

The most important issues at this stage were:

1. to verify that the institutional ethics committee abided by the ICH GCP standard;
2. to involve a qualified pharmacist; and
3. to verify that all laboratories involved worked according to the ICH GCP standards.

A qualified institutional ethics committee was found to be in place. The pharmacist hired ensured that drug shipments, storage,

labelling, dispensing and accountability met international standards. The laboratories involved were asked to document their standardized methods and to file written proof that those methods were updated regularly. Given the absence of a national quality control program for laboratories in Thailand, HIV-NAT also needed to verify that the laboratories regularly participated in internal and external quality control programs and that results of such exercises were documented and stored appropriately.

For data verification, HIV-NAT relied, and continues to rely, on medical student interns in their fourth year of training from Amsterdam and Sydney. Overall study conduct mostly is supervised by representatives of the sponsors of ongoing projects.

In order to start meeting the secondary goals of the organization, HIV-NAT organized a workshop on GCP and HIV Clinical Trial Management in February 1997 for personnel of interested potential study sites in Thailand. Lectures and workshops were provided by staff from the Thai Red Cross Society, NATEC, NCHECR and external experts.

Expansion

The first two studies, in retrospect, have been pivotal to the subsequent success and expansion of HIV-NAT, as they gave the organization the chance to show to two major pharmaceutical sponsors and the larger HIV community that the organization's goals could be met and that study conduct according to the ICH GCP standard is possible in Thailand.

Once the first two studies were ongoing and data were being generated and presented, interest in the research collaboration on the part of potential sponsors grew. The protocols were developed and submitted rapidly, and patients were recruited in a time span unheard of in the USA, Europe or Australia. This was due to the large number of eligible study participants in Thailand who had virtually no access to antiretroviral therapy elsewhere. The first study recruited all eligible participants within three months. The limiting factors were HIV-NAT's human resources and hospital logistics, rather than the number of interested candidates [often the limiting factor in the developed world].

Information dissemination

The Directors understood from the start that sharing study results on an ongoing basis with HIV treating physicians and local policy makers and at international meetings would serve the goal of contributing to the improvement of HIV treatment, but would also serve the organization itself. Presenting data on an ongoing basis means quite an effort in terms of data-management, data-analysis, frequent submission of abstracts, and preparation of presentations. However, it allows those interested in HIV-NAT's work to judge its merits, and allows the sponsors to observe returns on their investment.

Within one year after recruitment of the first patients, study results were presented at the International Conference on AIDS in Asia and the Pacific (ICAAP) in Manila and have since then been presented at local, regional and international meetings on a regular basis, either as posters or oral presentations. HIV-NAT is now a regular contributor to the annual meeting of the Royal Thai College of Physicians, to the bi-annual International Conference on AIDS in Asia and the Pacific (ICAAP), to the annual Conference on Retroviruses and Opportunistic Infections in the USA, and to the Australasian Society of HIV Medicine (ASHM).

Transparency

Representatives of potential sponsors regularly visit our offices, clinic and affiliated laboratories to gain an impression of the quality of trial conduct and to meet with the research staff and generally leave enthusiastically. The Regulatory Departments of the first two international pharmaceutical sponsors both sent audit teams in the course of the first two studies. As during most audits, certain issues were raised by the auditors regarding the conduct of the studies that needed attention or improving, but the auditors generally were satisfied with what they found.

Ongoing funding

More sponsors now are willing to invest in HIV-NAT studies and four more locally designed studies (protocols 003, 005, 006 and 007, see Appendix A) have been able to secure funding since then. HIV-NAT has been approached by the US National Institutes of Health as a participating site in one of their multinational studies. (An overview of

planned clinical trials is found at Appendix E.)

Study generated income and grants enabled HIV-NAT to make available in Bangkok most of the required personnel over the last three years, with the exception of paid study monitors. (An overview of the current HIV-NAT staff structure can be found in Appendix B.)

A grant by the F. Hoffmann-La Roche 'Blue Sky Initiative' enabled HIV-NAT to move into its own offices in April 1999 with access to a computer network, internet connection and a telephone switchboard. The organization is approaching financial self-sufficiency through study generated income and grants, and needs to rely less on financial and intellectual support from the founding organizations.

Further training and development

Since the start of operations, two of the research nurses, the data-manager and the statistician have received additional training by NATEC and NCHECR in Amsterdam and Sydney. HIV-NAT staff members regularly teach GCP at workshops initiated by HIV-NAT itself, local universities, the MOPH, WHO or pharmaceutical companies, and act as consultants in the region.

In 1998, HIV-NAT organized the first annual 'Bangkok Symposium on HIV Medicine', a three-day course with international speakers in the field of HIV care and research. The symposium was aimed at Thai and regional health care workers with limited access to international journals, information technology and international meetings. External sponsoring and grants enabled healthcare workers to travel to and attend the symposium.

Internal review

In November 1998, HIV-NAT organized its first annual retreat, which proved to be very successful and valuable. Ongoing and planned research activities were presented and discussed for two days by all HIV-NAT staff and additional NATEC and NCHECR experts, including statisticians and pharmacologists. At the end of the retreat, the strategy and planned activities for the upcoming year were finalized. One of the major decisions was that HIV-NAT would engage the services of a consultant to write a five year design document or business plan, as the

organizations involved agreed that they lacked the managerial and financial expertise to write such a document. This design document is finished and details the operational, organizational and financial plans of the collaboration for the next 5 years. It can be submitted to potential sponsors as part of a presentation package or as part of a research proposal.

HIV-NAT published its first annual report in January 1999, containing an overview of current and planned HIV-NAT studies and additional activities. (An overview of additional activities can be found at Appendix D.)

Advisory board

An independent International Advisory Board of 10 members was formed to review ongoing and planned studies, and the quality of the research on a yearly basis. The Directors agreed that the Advisory Board should represent acknowledged expertise in the field of HIV medicine, clinical trials, organization management and regulatory affairs and also the countries collaborating in HIV-NAT. Professor Lange and Professor Cooper each approached an independent, acknowledged expert in the field of HIV from the Netherlands and Australia. Professor Joost Ruitenbergh, Chairman of the Central Laboratories of the Netherlands Blood Transfusion Service, and Professor Peter McDonald, Head of the Department of Microbiology and Infectious Diseases, Flinder's University Medical Centre, Australia, both accepted a position on the Advisory Board. Professor Praphan approached the Secretary General and Assistant Secretary General of the Thai Red Cross Society, the head of the AIDS Division of the MOPH and the Head of the Thai Food and Drug Administration [FDA], who also accepted their appointments. The Directors together approached Professor Scott Hammer of Harvard Medical School, one of the leaders in the conduct of large, multi-center clinical HIV studies in the U.S.A. The Advisory Board is made up of these 7 plus the 3 co-directors of HIV-NAT, and is fortunate in having the advice of these experts.

Issues encountered

From the beginning, HIV-NAT has been presented with certain dilemmas unique to working in a setting with limited resources and potentially vulnerable study participants.

Guidelines

An important ethical dilemma arises from widely accepted ethical guidelines sometimes imposing demands on the conduct of clinical HIV research in Thailand that may seem diametrically opposed. The Declaration of Helsinki¹⁷, for example, demands that in any medical study every patient, including those of a 'control group' [if any], should be assured of the best proven diagnostic and therapeutic method. This would mean providing antiretroviral triple combination therapy (HAART), the current standard of care in developed countries. At the same time, the 'WHO International Ethical Guidelines for Biomedical Research Involving Human Subjects'¹⁸, which include the 'Declaration of Helsinki' as an appendix, state that research involving subjects in underdeveloped communities should be responsive to the health needs and priorities of those communities and should not exhaust resources which the community usually devotes to the health care of its members. This rules out using the very same triple combination therapy in the setting in which HIV-NAT is working.

This dilemma is not easily solved. HIV-NAT currently conducts studies that comply with either one of the above guidelines but which are, by definition, not in accordance with the other guideline. The economic and social realities of Thailand and the region may eventually change, but redistribution of wealth on a national and international level, and improved access to health care and health insurance, will take time. HIV-NAT's approach is an attempt to determine the maximum possible survival years of acceptable quality that can be gained with current funds available.

At the same time, HIV-NAT believes that it should not shun studies in the Thai population which use more advanced and expensive treatments. There are many reasons for this.

1. The individuals participating in such studies benefit from the treatments.
2. The treatments are affordable for some people in Thailand.
3. Local experience with advanced treatments is desirable as the available resources and the price of the treatments are not static.
4. The treatments may become more widely available. The price of new treatments often does come down when the demand for the drug and the production increase.
5. Well documented positive treatment results often mobilize lobbying movements to make drugs more widely available and sometimes can succeed in convincing policy makers to reallocate available funding [as was the case with the Brazilian Government's decision to make triple antiretroviral therapy available on a large scale in Brazil].

Long-term treatment

Another ethical dilemma stems from the need for long-term treatment for participants in the protocols.

Study participants in the first three protocols were clearly informed of the absence of any guaranteed follow-up treatment after the end of the one-year study period, both verbally and in the written information they received, and, as such, ICH GCP requirements were met. However, the majority of patients in the developed world participating in clinical studies under such conditions and restrictions have alternative means of treatment available after the study. This is not the case for the majority of study participants in Thailand and other developing countries.

This problem partly resolved itself in the course of time as HIV-NAT has been able to 'roll-over' study participants at the end of the first three studies to subsequent 'follow-up' protocols that are of sufficient interest to the participants, the researchers and the sponsors.

Until now, no patient has been denied some form of follow-up study treatment. These treatments, however, are often sub-optimal

when compared to the standard of care offered in developed countries and the organization keeps searching for more permanent solutions to this problem.

Sponsor commitment

With the growing interest of sponsors in HIV-NAT, the ‘bargaining power’ of the organization has increased and the pharmaceutical company Merck Sharp & Dohme was the first sponsor to commit to supplying its drug for former study participants for as long as treatment is deemed beneficial by the treating physician. The Thai MOPH is also supportive and may commit to providing antiretrovirals (made available to them at a reduced price by the pharmaceutical industry) for a period of five years for participants in a study designed and otherwise sponsored by the US National Institutes of Health with the immunomodulator interleukin-2 (IL-2). The pharmaceutical company Boehringer Ingelheim has recently committed to providing two years of triple combination follow-up therapy for participants after completion of a study.

These precedents are making it less difficult to convince other sponsors that they cannot simply count on the participants, the Thai government, and HIV-NAT to take on the burden of trying to provide follow-up treatment for former study participants.



Nurses at the new building

Partnerships and alliances

Of great importance to the success of HIV-NAT has been:

1. the partnership between the three founding organizations;
2. the relationship with the AIDS Division of the Thai MOPH;
3. the relationship with local patient organizations; and
4. the relationship with the sponsors.

Founders

The three founding organizations have kept their promises as written in the Statutes and have remained pro-actively involved since the start of the organization. The visits of HIV-NAT staff to NATEC and NCHECR has resulted not only in gained expertise but also has achieved cross-cultural and cross-boundary bonds enabling direct lines of communication. At the same time, visits by NATEC and NCHECR staff to HIV-NAT have increased sensitivity to the particular problems experienced by a starting organization in a less developed country. All exchange visits take place in the context of educational activities benefiting HIV-NAT, and although HIV-NAT needs to rely less and less on support from Amsterdam and Sydney, help is still only an e-mail away.

MOPH

In the course of time, HIV-NAT has built up a strong relationship with the AIDS Division of the Thai MOPH, whose leaders have met virtually all expectations the Directors had of the AIDS Division when HIV-NAT started operations.

This positive relationship is based on the complimentary nature of HIV-NAT and MOPH. The AIDS Division of MOPH oversees a huge network of clinical HIV treatment sites in Thailand and therefore has the capacity to conduct clinical studies requiring large numbers of patients, such as clinical endpoint studies. Due to the size and expense of such an undertaking, and due to the relative inexperience of most Thai sites, such studies demand considerable preparation and time, and hypothesis generating input is needed to develop sensible and cost-effective

tive research protocols. HIV-NAT, being small in comparison, can conduct smaller studies with virological or immunological endpoints relatively quickly and provide exactly such input. Also, with clinical endpoint study data pending, data from HIV-NAT studies can be used for formulating national treatment policy for the time being. The expertise gained by sites participating in HIV-NAT studies may subsequently benefit larger national studies.

Patient organizations

HIV-NAT has been fortunate in that the largest organized group of people living with HIV (PWH) in Thailand, the Wednesday Friends' Club, is part of the Thai Red Cross AIDS Research Centre of which HIV-NAT is also a branch. This means that lines of communication with the population most affected by HIV are short and that criticism and suggestions of our PWH colleagues can easily be incorporated into HIV-NAT's operations and future



Wednesday Friends Club and friends

projects. At the same time, the Wednesday Friends' Club members work as peer educators who make HIV-NAT's research and its purposes widely known among PWH. (A selection of Case Interviews with PWHs can be found at Appendix C.)

Sponsors

From the outset, HIV-NAT has aimed to foster good and lasting relationships with the pharmaceutical industry. By adhering to the study protocols and promptly reporting serious adverse events experienced by study participants, and through an ongoing sharing of study results and related information, HIV-NAT has built up credibility with the sponsors. This credibility has resulted in funding being made available for accommodating the expanding research staff and a willingness on the part of the sponsors to consider the dilemmas presented to them by HIV-NAT, such as the problematic provision of follow-up medication for study participants in Thailand. The maintenance of good relationships with spon-

sors is essential for the continuance of HIV-NAT and its projects. The active support of Bristol–Myers Squibb, Boehringer Ingelheim, GlaxoWellcome, Merck Sharp & Dohme and Roche is acknowledged and greatly appreciated.

Monitoring and evaluation

Currently, no formal overall evaluation of HIV-NAT and its activities is available. However, some clear indications are evident.

1. 9 clinical studies and several basic research projects have been instigated.
2. 450 participants currently are enrolled in HIV-NAT studies and are being provided with effective treatment through these protocols. Another 450-500 participants are anticipated to enrol in studies in preparation.
3. Participation of adults in studies is almost equally divided between males and females. A safety, tolerability and pharmacokinetic study has commenced with HIV-exposed infants.
4. Numbers of participants lost to clinical follow-up is low (3%-10%), even after more than 3 years of study participation.
5. The audit report of the conduct of the first research study was generally positive.
6. So far, all submitted abstracts to international HIV meetings have been accepted. Acceptance of abstracts for such meetings is based on a rigorous peer-review selection procedure.
7. Informal evaluation forms submitted by participants of the GCP work shops and the annual Bangkok Symposium on HIV Medicine are positive and indicate a clear need for these activities.
8. Study sponsors often actively pursue HIV-NAT with study proposals, rather than HIV-NAT looking for sponsors.
9. Sponsors now demonstrate willingness to invest in the organization by financing infrastructure and by sponsoring the presentation of study results at international meetings.
10. The majority of study participants earn less than THB 5,000 (US \$ 130.-) per month. Their access to antiretroviral treatment elsewhere is limited. However, many are professionals or government

employees who perceive that they may receive more potent treatment, better service and information from well informed health care workers by participating in a clinical trial. Many of these participants use the trial period for saving resources for later treatment.

Lessons learned

In its three years of operation, HIV-NAT has learned that:

- 1) Clinical trials can be conducted according to Good Clinical Practice guidelines in Thailand and should be feasible in other settings outside of the western world.
- 2) With support from existing overseas clinical HIV research organizations and the local MOPH, an HIV clinical research organization was able to be set up in Thailand within three years. The organization is financially nearly self supporting through its study generated income and grants, and needs to rely less and less on financial and intellectual support from the founding organizations.
- 3) One needs to dare make a start. The income generated by the first two studies barely paid for the expenses, but study generated income has gradually increased over time. For two studies that are about to start, HIV-NAT will receive financial compensation equal to the amount received by participating sites in the same projects in Europe, Australia and the US. This increase in income has allowed the organization to grow in terms of staff and other resources, such as additional education for staff and improved office facilities which in turn improve the overall quality of study conduct.
- 4) For the first three protocols, HIV-NAT was unable to guarantee follow-up medication to participants upon initiation of the studies. Now, all interested participants have been able to enrol in follow-up protocols, after the sponsors' confidence in our work grew and enthusiasm for our activities increased. For three later studies, HIV-NAT has been able to obtain longer-term drug availability guarantees, either directly from the sponsors or through a reduced pricing scheme.
- 5) Clinical trials do create access to effective drugs, but only for a limited number of people considering the efforts and resources invested. Gaining access to treatment for patients may therefore not be the correct primary reason for participating in clinical research.

- 6) Clinical trials are labour intensive anywhere, but even more so in a setting where not all those involved are thoroughly familiar with clinical research. The coordinating center needs to have enough manpower and time available. The following aspects stand out from the HIV-NAT experience:
- a) Adequate personnel willing to learn new skills need to be available at any research site to make the research succeed. HIV-NAT has learned that without dedicated staff and a responsible study coordinator present at every individual research site, the effort is often doomed. For many staff members at satellite sites, conducting the study is only one of many duties and clinical studies are, by definition, a multi-disciplinary effort.
 - b) Not all parties involved in conducting clinical research in the developing world abide by the ICH GCP standard. Since the majority of sponsors will demand this standard to be met, a clinical research organization working in such a context will have to facilitate, for example, the local ethical committees, laboratories, or the local pharmaceutical representatives in working as closely with ICH GCP as possible. Often ad hoc consultation and education sessions and administrative improvisation will be required.
 - c) Sponsors want to be convinced first of the likelihood of a study being conducted in accordance with ICH GCP. Sites need to invest more time in interaction and negotiations with the sponsors prior to a study. HIV-NAT has recognized the need to invest more time in sponsor site visits and accepts that HIV-NAT studies, for the time being, are more likely to be audited by the sponsor.
 - d) The uncertainty regarding follow-up medication for many study participants forces HIV-NAT to maintain active negotiations with the sponsors and other parties involved on this issue.
- 7) In addition to Thailand's economic reality, limited access to anti HIV-drugs in Thailand is due to a relatively slow registration process of newly available anti-HIV agents, relatively long and often unpredict-

able regulatory approval procedures, and a sometimes passive attitude on the part of some local pharmaceutical company representatives. HIV-NAT has learned that by initiating studies in collaboration with the companies' international headquarters, the local representatives are forced into a pro-active import approach. Through HIV-NAT's research activities and by generating local data which are ethnically applicable, pressure is being exerted on government agencies, regulatory authorities and ethical committees to re-evaluate their tasks and performance in the areas of HIV care, clinical research and importation and provision of drugs.

- 8) Given the predominance of the English language in HIV clinical research and in doing business with the sponsors, having staff members available who are fluent in English is essential.
- 9) Despite the tremendous human resources and know-how available within the three founding organizations, few of its staff have a managerial or financial background. Involving a consultant with such a background to write a business plan for HIV-NAT has proven very useful. Rather than focussing on scientific study content, the consultant's focus is on management issues, long-term potential, and accountability of resources from an outsider's perspective. Such observations and experience have initiated a managerial and logistical streamlining at HIV-NAT.
- 10) Maintaining an open and ongoing communication structure within the organization and with study participants, our collaborators and the study sponsors benefits all parties involved.

The future

HIV-NAT hopes to expand its activities in Thailand and the region and has faith in the ability of the staff at HIV clinical sites in Thailand to participate in clinical research. HIV-NAT's efforts, and all clinical research in Thailand, would be facilitated by the issuing of national ICH GCP based guidelines for local institutional ethical committees and making ICH GCP conduct mandatory in Thailand. The establishment of a national quality control and assurance program for laboratories, mandating participation by all laboratories, would greatly facilitate clinical research efforts in Thailand.

The biggest issue posing a potential threat to expansion remains uncertainty regarding follow-up treatment for study participants. The HIV patient population of a participating site expands when effective medication becomes available through studies. Sites are willing and able to cope with this increased caseload as long as patients can remain largely asymptomatic due to the treatments received. However, when no follow-up medication is available, sites may soon be dealing with larger numbers of symptomatic patients for whom the available resources need to be spread thinner than would have been the case when the site had not participated in the research project. The reluctance of some investigators to participate in research under such circumstances is understandable. So is the reluctance of sponsors to commit to life-long support of potent drugs for former study participants given the numbers of patients involved, the price of the medications and the precedent it may set internationally.

References

1. Rojanapithayakorn W, Hanenberg R. *The 100% Condom Program in Thailand*. AIDS 1996; 10:1-7
2. Surasiengsunk S, Kiranandana S, Wongboonsin K, et al. *Demographic impact of the AIDS epidemic in Thailand*. AIDS 1998, 12(7):775-84
3. Shaffer N, Chuachoowong R, Mock PA, et al. *Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial*. Lancet 1999; 353:773-780
4. Brown T, Sittitrai W. *The Impact of HIV on Children in Thailand*. Program on AIDS, Thai Red Cross Society, June 1995
5. CDC, Division of AIDS; data presented at the National AIDS Committee Meeting, September 1, 1999
6. Ahuje et al. *Everyone's Miracle?* World Bank, 1997
7. *World Development Indicators*, World Bank, 1998
8. *Poverty Monitoring Database*, World Bank, April 1999
9. Prescott N, Kunanasont C, Phoolcharoen W, et al. *Formulating rational use of antiretrovirals in Thailand*. XI International Congress on AIDS, Vancouver, Canada, July 7-12, 1996
10. Sahai H, Khurshid A, Ageel MI. *Clinical trials: an overview*. Appl Clin Trials 1996, 5:30-48
11. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Harmonized Tripartite Guideline, *Ethnic Factors in the Acceptability of Foreign Clinical Data*, February 1998
12. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Topic E6, *Guideline for Good Clinical Practice*, Step 5, Consolidated Guideline 1.5.96, ICH Harmonised Tripartite Guideline, January 1997
13. Fischl M, Parker C, Pettinelli C et al.: A randomised controlled trial of a half daily dose of zidovudine in patients with the acquired immunodeficiency syndrome. N Engl J Med 1990, 323(15):1009-1014
14. Collier A, Bozzette S, Coombs R. et al.: *A pilot study of low-dose zidovudine in human immunodeficiency virus infection*. N Engl J Med 1990, 323(15):1015-1021.
15. Kimura S, Oka S, Toyoshima T, et.al.: *A randomised trial of half doses of azidothymidine in Japanese patients with human immunodeficiency virus type 1 infection*. Intern Med 1992, 31(7):871-876.
16. Nordic Medical Research Council's HIV Therapy Group: *Double blind dose-response study of zidovudine in AIDS and advanced HIV infection*. Brit Med J 1992, 304(6818):13-17.
17. World Medical Association Declaration of Helsinki, Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, last amended during the 41st World Medical Assembly, Hong Kong, September 1989
18. International Ethical Guidelines for Biomedical Research Involving Human Subjects, Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), Geneva 1993

Appendix A:

Clinical Trials

003

A randomized, open label, comparative trial of AZT/3TC vs AZT/3TC/ddl in antiretroviral naïve HIV-1 infected Thai patients.

To evaluate tolerability and comparative virologic and immunologic efficacy of AZT in combination with 3TC vs AZT in combination with 3TC and ddl.

005

A randomized, open label, comparative study to evaluate the efficacy and tolerability of indinavir/low-dose ritonavir BID vs indinavir TID as part of combination antiretroviral therapy with Combivir™ (AZT/3TC) for the treatment of HIV-1 infection in an antiretroviral pre-treated Thai population.

To assess the efficacy of the two drug regimens on HIV-1 viral load as measured by HIV-1 RNA quantification in plasma.

To assess the efficacy of the two drug regimens on immune responses as measured by peripheral CD4+ lymphocyte counts.

To assess safety and tolerability of the two regimens.

006

A phase II, randomized, four arm, open label, comparative trial to evaluate the efficacy and tolerability of combination antiretroviral therapy with ddl+d4T alone or in combination with either nevirapine, hydroxyurea or both nevirapine and hydroxyurea for the treatment of HIV-1 infection in a Thai study population.

To compare time weighted change in plasma HIV-1 RNA from baseline as a measure of efficacy and to assess safety and tolerance of the four arms.

To evaluate the time weighted change in absolute CD4+ cell counts and CD4/CD8 ratio from baseline in each regimen and to assess

efficacy of the different regimens on survival and HIV disease progression.

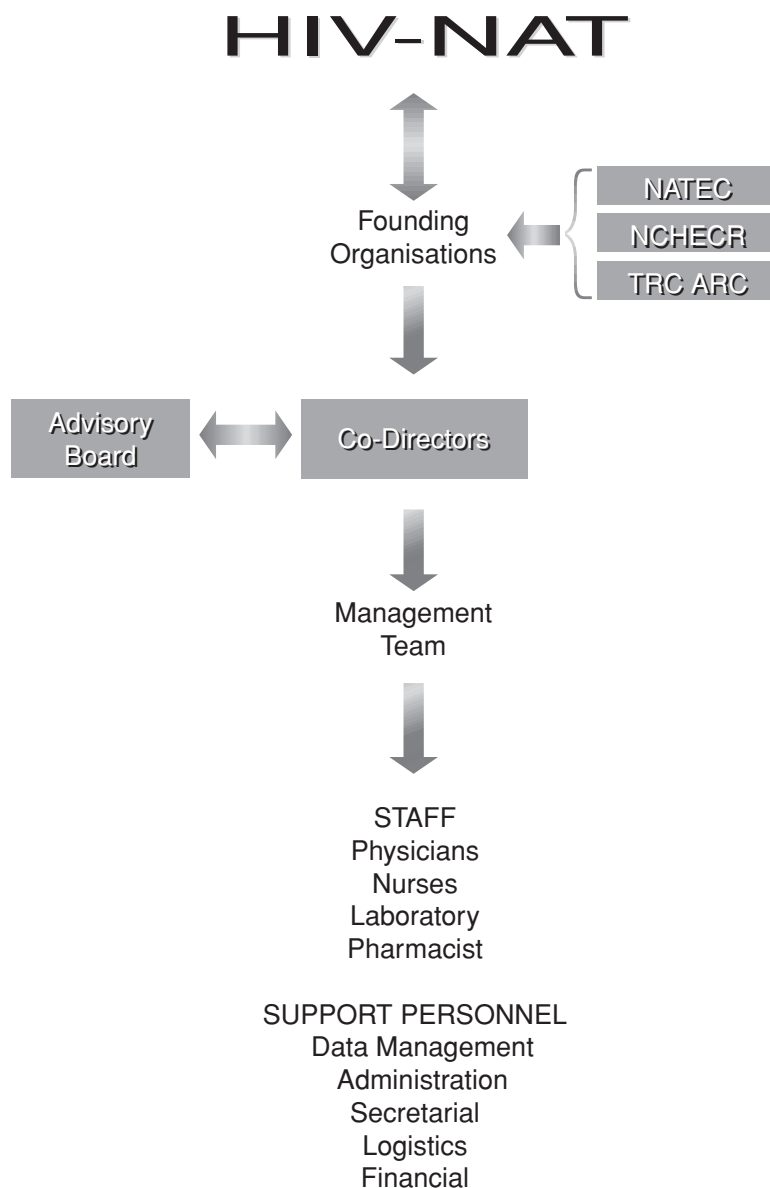
007

A study of the safety, tolerability and pharmacokinetics of nelfinavir co-administered with stavudine (d4T) and didanosine (ddl) in HIV-exposed infants.

To assess the safety and tolerability of the triple combination regimen of nelfinavir, d4T and ddl in HIV-exposed newborn infants.

To determine the appropriate dosage of nelfinavir and to assess its pharmacokinetics when given in combination with d4T and ddl in HIV-exposed newborn infants.

Appendix B: Organisation Structure December 1999



Appendix C:

Case Interviews

Random HIV-NAT study participant interviews, conducted throughout September 1999, in the research clinic waiting rooms. Ten verbally consenting participants were interviewed out of fifteen subjects who were approached. Therefore, bias cannot be excluded. Interviews were conducted by Mr. Sanya Umasa, the chairman of the 'Wednesday Friends Club' of the Thai Red Cross AIDS Research Centre, an organization run for and by PWH. Mr. Sanya informed the interviewed participants of his independent position and of the fact that the interview text would only be anonymously made available to HIV-NAT research staff. Interviews were translated and edited from Thai to English by Mr. Sanya Umasa and Dr. Eugene Kroon.

Client 1: male

I have now participated in clinical trials for 7 years. I know about the projects through Bumrungrad Hospital where Professor Praphan works as well. I have taken part in many studies already. Every time a study ended, I immediately enrolled in another study. At the moment, I take three drugs; AZT, ddI and Ritonavir, plus cotrimoxazole as PCP prophylaxis. Before I join the studies, I make sure I clearly understand the patient information received. Since I have been participating in studies, my knowledge about HIV/AIDS has increased and since I have been taken anti HIV medications my health has improved. I would like to remain on clinical trials forever.

Also, the study staff gives me information about issues such as how to prevent myself from being (re-)infected by another subtype of the virus or how to keep the virus under control as well as possible. I follow the doctor's instructions very strictly and I take my medications without interruption. This project is good. There is no need to improve it as it has improved my wellbeing. If I was not enrolled in this study, I don't know what I would be doing right now.

Client 2: female

This is my third year 'on-study' as I started taking part in 1996. I came to the Thai Red Cross Anonymous Clinic and saw the doctor who told me about the HIV-NAT studies. Before having to decide whether or not to join the study, the nurse and physician explained all the details to me. When I started participating, I hoped I would improve. Since I joined the study, I have been taking three drugs together. I now understand HIV/AIDS better and for the moment I feel mentally great. The study staff gives good advice and when this project is over I hope I can enrol in another study. For that matter, I hope there will be new studies to enter all the time. If there would be no more studies, I don't know if I would have the strength to go on as I would not know where to get drugs outside of clinical trials. The only problem for me is that I need to come here frequently as my house is far away.

Client 3: male

I came to have my blood tested at the Thai Red Cross Anonymous Clinic in 1998. Once I knew I was HIV positive, the doctor told me about HIV-NAT and told me that there was a study that was still recruiting for which I might be eligible. I asked for more information about the project and when the doctor started telling me about it, I already knew I wanted to join. After I enrolled, I learned more about HIV/AIDS. The service of the study staff is good and they are very kind to the patients. Right now, I take AZT, 3TC and Saquinavir. When the first project ended, the staff told me about a new project I might join and I decided to enrol again. If there were no studies, I would not have the opportunity to take anti HIV medication. There is one thing that this project should improve: they should expand more to the provinces outside Bangkok. Right now, people in the provinces have less chance of joining while they are already poorer.

Client 4: male, 30 years

Right now, I take part in study HIV-NAT 005. Previously, when I was being treated in Bamradnaradun Hospital and Vachira Hospital, I did not know about HIV-NAT. I came to know about HIV-NAT through the Wednesday Friends' Club and I am currently being treated in

Chulalongkorn Hospital. Before enrolling in study 005, I took AZT and ddI for almost 1 year. After finding out about the HIV-NAT studies, I had to wait for about 3 months before I could enrol in one. I received a lot of information before joining the project and right now I take Combivir and Crixivan. Besides receiving the medication, I receive health checks for possible medication side effects such as diabetes, kidney stones and others. If I were not enrolled in the study, my health would not be monitored like this. The HIV-NAT staff service is excellent. I am happy that I could enter the project because otherwise I would have continued taking AZT/ddI and sooner or later become resistant to those drugs. I could not afford a protease inhibitor. I would like to be able to enrol in another project after this one finishes to maintain my health as is.

Client 5: male, 35 years

I have been infected since 1993, but when I got infected I didn't know anything about the virus or AIDS at all. Previously, I was treated at the Police Hospital. Since 1996, Dr. Matana has treated me at the immune clinic of Chulalongkorn Hospital. I understand more about HIV and AIDS since having taken part in Dr. Matana's TB study. However, after that study was over, I didn't take any medication at all, until I had the chance to talk with study nurse Khun Mena who told me about HIV-NAT and study 005. I was willing to join the study and I waited for about three months until I could join. I received a lot of information about the study from the study staff before I joined. Right now, I take Indinavir, Ritonavir and Combivir. I do not experience any side effects so far. Since enrolling in this study, I have learned more about opportunistic infections and the possible side effects of the medications I take, such as kidney stones, but that didn't stop me from taking the drugs. The service of the study staff is usually okay. I would like for HIV-NAT to provide information about side effects to more people, such as HIV infected people outside the studies. I would like to enrol in a new study after this one finishes.

Client 6: female

I have been taking part in this study for 2 years. Before I joined, I went to the Thai Red Cross Anonymous Clinic to have my blood checked. After I was found to be HIV-positive, the doctor told me about this project. I was interested and therefore asked the doctor for more

details. When I knew everything I wanted to know, I decided to enrol in the study. Before talking with the study staff and enrolling, I knew nothing about HIV/AIDS. Since participating in the study, I understand HIV/AIDS better. The HIV-NAT staff explains things I don't understand. Right now I take three drugs; Abacavir, Stavudine and Lamivudine, and I never miss a dose. The HIV-NAT staff service is excellent and I think that if I could not have entered the study I would have felt pretty hopeless and desperate by now. Since entering the study, I have hope that I'll stay alive because I have access to medication. The only problem for me is that I don't get enough sleep coming here. My home is far away and I have to get up very early.

Client 7: male, 36 years

I know that I am HIV-positive since 1997 when I had a skin rash all over my body. I went for treatment to Bumrungrad Hospital and was treated by Dr. Matana. She advised me to continue treatment at Chulalongkorn Hospital where I got two medications, AZT and ddI. My skin problems disappeared since taking the medications but in early 1999 I had the same symptoms again. I tried to get my skin cured, but the rash wouldn't go away. I thought it was my time to die already because the virus was starting to get resistant to the drugs I was taking. I had no money to change to new drugs, as they are very expensive. From the doctor at Chulalongkorn Hospital, I learned about project 005 and I decided to apply to join. I did not have to wait too long and started taking my new medications in July 1999. I now take Indinavir and Combivir. I have the feeling I died already but was reborn again and it is a very good project. I hope there will be projects to follow for a long time to help people stay alive a lot longer. The service of the study staff is very good. They seem to understand HIV-positive people. They give strength and don't discriminate. I also learned more about HIV medicine and opportunistic infections.

Client 8: male, 29 years

I know that I am infected with HIV since 15 February 1999 when I had a skin rash and fever off and on for many days. I went to see the doctor and asked him to check my blood for HIV. I took AZT and ddI for some months, but I didn't have money to keep buying the drugs, as

they are very expensive. From a friend, I knew there was an immune clinic in Chulalongkorn Hospital, so I went there for treatment and I continued to take AZT and ddl with support from the hospital's social services department. I know about HIV-NAT from the Wednesday Friends' Club who told me that Khun Mena of HIV-NAT had offered a new study at the immune clinic for interested patients. I was interested in the study and after 2 months of waiting I joined. Right now, I take Indinavir and Combivir. I think the project is very good as I save the money I previously spent on treatment and I could not really afford the drugs by myself. Before entering the study, the nurse explained all the details and I signed an informed consent. I think the study staff is generally very good.

Client 9: male, 37 years

I know I have been infected since 1993, but when I found out, I did not know where to go for treatment. After a year, I went for treatment to Bumrungrad Hospital where I was Dr. Praphan's patient. I started taking AZT and ddl and I took those drugs for 2.5 years. Later on, I stopped taking the drugs since I had no money to pay for them. I transferred to get treatment at Chulalongkorn Hospital, as advised by Dr. Praphan. I have been a patient at Chulalongkorn Hospital since 1998, but I could not take any medication, as I still didn't have any money to spend on drugs. At some point, I went to get my CD4 count checked at the Thai Red Cross Anonymous Clinic and the staff there told me there was a HIV-NAT project starting soon. I was really interested to join the project because I like to take medication in order to prolong my life. Before entering the project, I read the details in the patient information form and one of the staff explained briefly about the advantages and disadvantages. I think that the staff and the physicians take care of the patients well, which I appreciate. But some of the hospital staff seem to have something against HIV patients and that should be improved. I don't feel that way about the nurses and the doctors at HIV-NAT. Right now, I take three drugs; Combivir, Indinavir and Ritonavir. At first I experienced a lot of side effects. Now they are starting to improve. When this project ends, I would like to enrol in another project.

Client 10: male, 35 years

I know that I am HIV positive since 1998. I used to receive treatment at Vachira Hospital. The first six months that I knew I was infected, I took AZT and another treatment for some opportunistic illness. As I continued to take AZT, the virus became resistant to the drug and my CD4s were down to 10/microL. I then took AZT together with ddI but did not improve. My CD4s went down to 7/microL. I kept taking the drugs as I did not know what else to take. I also knew that new drugs would be more expensive. I knew about HIV-NAT for a long time, but did not know in detail how to enrol in the studies. I knew was that if I could enter I would get drugs for free. This I knew from the Thai Red Cross Anonymous Clinic staff and their social service staff. When I found out more about the study methods, I was interested in enrolling in a study and I went for an interview with HIV-NAT staff. As I turned out to be eligible for a project, the staff explained about the study in more detail. Right now, I take Combivir, Ritonavir and Indinavir. The HIV-NAT staff provides good service. As well as providing medication, the staff counsels me. I think the staff will take care of me like this after the project is over. Maybe there will be an opportunity for patients already enrolled to continue in another project. Subsequently, I would like to enrol in another project.

Appendix D:

Other Activities

One of the objectives of HIV-NAT is to serve as a training centre for HIV clinical studies in Thailand and the region. From the start of the organization, the following activities (other than clinical studies and related basic research) have been undertaken.

Feb - Mar 1997

Workshop on Management of Multi-centre Clinical Trials, Kanchanaburi. Target group: potential future study sites in Thailand. Attended by 80 participants from 10 Thai sites. Lectures contributed by speakers from Thailand, the U.S.A., Hong Kong, Australia, and the Netherlands.

Aug 1997

Workshop on Good Clinical Trial Practice (GCP) for Nurses, held in Bangkok. Target group: nurses from potential future study sites in Thailand. Attended by 24 participants from 5 centres in Thailand and the AIDS Division of the Ministry of Public Health. Lectures contributed by staff members of HIV-NAT and Roche (Thailand) Ltd.

Dec 1997

HIV-NAT staff answer telephone questions from viewers watching a Thai television program on World AIDS Day.

Dec 1997

Three HIV-NAT staff members contribute six lectures to a GCP workshop organized by the AIDS Division of the Ministry of Public Health.

Jan 1998

The 1998 Bangkok Symposium on HIV Medicine. Target group: Thai and regional physicians entering the field of HIV medicine with as yet limited experience. Attended by 189 participants. Lectures contributed by speakers from Thailand, the U.S.A., Australia, and the Netherlands.

July 1998

AIDS phonecare line opened by the AIDS Research Centre, Thai Red Cross Society. HIV-NAT nurses help answer questions from callers related to HIV/AIDS.

Jul 1998

HIV-NAT staff contribute to a workshop organized by Chulalongkorn University to upgrade the GCP standard in Thailand. Target group: other universities, research groups and pharmaceutical company representatives.

Sep 1998

Workshop on Good Clinical Research Practice (GCP) for HealthCare Workers in HIV/AIDS. Organized by HIV-NAT at the request of the Thailand HIV/AIDS ambulatory care project. Target group: staff involved in HIV clinical research conduct at Bamrasnaradura Hospital, Nonthaburi. Lectures contributed by staff of HIV-NAT and Roche (Thailand) Ltd.

Oct 1998

HIV-NAT staff participate as part of a panel to answer questions by telephone from viewers during a television program about HIV infection.

Nov 1998

Lecture on the Role of the HIV Clinical Research Pharmacist. Target group: interested pharmacists and local pharmaceutical company representatives. Lecturer Ms. Heather Leake from Brighton, UK.

Dec 1998

HIV-NAT staff contribute lectures to a course in Phuket for HIV (trial) physicians on the use of the internet and high-tech presentations. The intention was that participants would return to train colleagues at their respective sites.

Jan 1999

The 1999 Bangkok Symposium on HIV Medicine. A total of 280 participants from India, Indonesia, Malaysia, Philippines, Taiwan and Thailand. Lectures provided by faculty from Thailand, the U.S.A., Australia and the Netherlands.

Nov 1999

At the invitation of the Joint United Nations Program on HIV/AIDS (UNAIDS), HIV-NAT staff submit the first draft of HIV-NAT, the HIV Netherlands Australia Thailand HIV Research Collaboration, Thai Red Cross AIDS Research Centre, to be published as part of their Best Practice publication series.

Dec 1999

Workshop on Good Clinical Practice Pre-trial Training. Target group: 16 study sites (MOPH hospitals) in Thailand which will participate in the ACTT 002 study, an antiretroviral study conducted by the AIDS Division, Ministry of Public Health and HIV-NAT. Attended by some 65 nurses, physicians, laboratory staff and pharmacists of the participating sites. Lectures and workshops provided entirely by HIV-NAT staff.

UNAIDS/WHO Collaboration

During 1999, Dr Chris Duncombe from HIV-NAT acted as a consultant for the World Health Organisation (WHO) in Vietnam and Cambodia.

In Vietnam, the consultant visited Hanoi and Ho Chi Minh City to assess current standards of clinical care for patients with HIV infection. Future priorities identified in the report included training of HealthCare workers, particularly in the field of opportunistic infections,

the appropriate use of anti-retroviral agents and the prevention of mother-to-child HIV transmission.

In Cambodia, previously written draft guidelines for the management of HIV-infected adults and children and home and community care were reviewed during a consensus workshop in Phnom Penh, to finalise the guidelines for publication and distribution throughout Cambodia.

It is anticipated that further collaboration will occur in 2000.

Appendix E:

Planned Clinical Trials

ESPRIT

Description:	A randomised, open-label, phase III international study of subcutaneous recombinant IL-2 in patients with HIV-1 infection and CD4+ cell counts $300/\text{mm}^3$.
Status:	Scheduled to commence in 2000
Sites:	5 sites in Thailand
Study Population:	4000 patients worldwide (300 patients in Thailand)

AI424-008

Description:	Evaluation of the safety and antiviral efficacy of a novel HIV-1 protease inhibitor, BM232632, in combination with d4T and 3TC as compared to a reference combination regimen.
Status:	Scheduled to commence in 2000
Sites:	54 sites worldwide
Study Population:	400 patients (minimum 15 patients from HIV-NAT)

2NN

Description:	An open-label comparative study to evaluate the short-term antiviral efficacy of nevirapine and efavirenz in combination with d4T and 3TC.
Status:	Scheduled to commence in 2000
Sites:	18 sites worldwide
Study Population:	450 patients (30-60 patients from HIV-NAT)

E-1696

Description: A multi-centre, double-blind, randomised trial to compare the effects of nandrolone decanoate and placebo on body composition and bodyweight in HIV-positive men with mild to moderate wasting, with Sustanon 250 as active reference treatment.

Status: Scheduled to commence in 2000

Sites: 21 sites worldwide

Study Population: 300 patients (minimum 20 patients from HIV-NAT)

Drugs Glossary

ABC	abacavir
ART	anti-retroviral therapy
ddl	didanosine
EFV	efavirenz
HAART	Highly Active Anti-retroviral Therapy
HU	hydroxyurea
IND	indinavir
IL-2	interleukin-2
3TC	lamivudine
Combivir®	lamivudine+zidovudine
NLF	nelfinavir
NVP	nevirapine
NNRTI	non- nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
RTV	ritonavir
SQV	saquinavir
SQV-SGC	saquinavir soft-gel capsules
d4T	stavudine
ddC	zalcitabine
AZT	zidovudine

The Joint United Nations Programme on HIV/AIDS (UNAIDS) is the leading advocate for global action on HIV/AIDS. It brings together seven UN agencies in a common effort to fight the epidemic; the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), the United Nations Population Fund (UNFPA), the United Nations International Drug Control Programme (UNDCP), the United Nations Educational, Scientific and Cultural Organization (UNESCO), the World Health Organization (WHO) and the World Bank.

UNAIDS both mobilizes the responses to the epidemic of its seven cosponsoring organizations and supplements these efforts with special initiatives. Its purpose is to lead and assist an expansion of the international response to HIV on all fronts: medical, public health, social, economic, cultural, political and human rights. UNAIDS works with a broad range of partners – governmental and NGO, business, scientific and lay–to share knowledge, skills and best practice across boundaries.

Produced with environment-friendly material



Joint United Nations Programme on HIV/AIDS

UNAIDS

UNICEF • UNDP • UNFPA • UNESCO
UNDCP • WHO • WORLD BANK

Joint United Nations Programme on HIV/AIDS (UNAIDS)
20 avenue Appia, 1211 Geneva 27, Switzerland
Tel. (+41 22) 791 46 51 - Fax (+41 22) 791 41 65
e-mail: unaids@unaids.org – Internet: <http://www.unaids.org>