HIV-NAT

Promoting Rational and Evidence-based Use of Antiretroviral Therapies

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Introduction

Scientifically robust clinical research conducted in an ethical manner consistent with good clinical practice guidelines is a critical pre-requisite for evidence-based medicine and policy development. Moreover, randomized controlled trials and cohort studies contribute to the more rational (safe, effective and cost-effective) use of medicines, thereby informing clinician judgments about individual patients and also improving the health outcomes of the population. Since the HIV virus was identified in the 1980’s, the pharmaceutical industry invested much activity in finding drugs with antiretroviral activity.

Much of the clinical research activity to find agents to treat or cure HIV infection was initially concentrated in the Western world. However, the global burden of HIV disease is disproportionately represented in resource limited settings (RLS). In many of these settings, access to antiretroviral therapy (ART) has been poor, and deaths from AIDS continue to rise. Individual socio-economic circumstances coupled with the relatively high cost of ART is one barrier to drug access, but structural factors also impede the delivery of ART to people in RLS. These factors include poor access to voluntary counseling and testing, limited public health infrastructure to support clinical and laboratory diagnosis and monitoring, and a lack of personnel and local experience to initiate and monitor treatment and toxicity.

Global efforts have more recently combined to increase availability and access to ART in RLS. However, to ensure evidence-based and rational use of ART, it is important to conduct locally relevant research designed to answer clinically relevant questions. In the 1990s, some HIV clinical trials were taking place in RLS, but fund providers were reluctant to invest heavily in this research because they questioned whether the research could be conducted in accordance with exacting international standards.

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The HIV Netherlands, Australia, Thailand Research Collaboration (HIV-NAT) was established in 1996 as a collaboration between The National Center in HIV Epidemiology and Clinical Research (NCHECR), Sydney, Australia, The International Antiviral Therapy Evaluation Center (IATEC), Amsterdam, The Netherlands and The Thai Red Cross AIDS Research Centre, Bangkok, Thailand. The directors of these organisations firmly believed there was an urgent need to advance ART research in resource limited settings. The aims of the newly formed organisation were to conduct clinical research into HIV/AIDS antiretroviral drugs and vaccines, and to develop and promote appropriate and affordable treatment strategies for people with HIV in Thailand and neighboring countries.4

On the 10th Anniversary of HIV-NAT we reflect on the way HIV-NAT has pursued these objectives and some of the important clinical and public health outcomes of the clinical research which has been conducted at HIV-NAT. State of the art clinical trials can be successfully conducted in resource-limited settings.

Thai and international divisions of three major pharmaceutical companies agreed to sponsor the first two trials at HIV-NAT.5, 6 Successful implementation of these early trials provided strong evidence of HIV-NAT’s ability to meet international standards of good clinical practice. Subsequently, in addition to initiating its own protocols, HIV-NAT began to receive invitations to participate in international multicentre trials initiated by external funders.7-10

Since these early trials, HIV-NAT has enrolled more than 1999 adult and paediatric participants in over 30 clinical trials, and established a clinical research network with over 20 sites in Thailand. Patients who enrolled in the first clinical trials with over nine years of follow-up data are still treated at our centre. With the start of the PREDICT study of immediate versus deferred initiation of ART in Children,11 our clinical research network has expanded to include two sites in Cambodia. HIV disease progression can be retarded in a resource-limited setting to the same degree as achieved in developed countries.

In a cohort analysis of some of the early HIV-NAT studies with 1677 person years of follow-up, the progression rate to AIDS was 1.4 (95% confidence interval [95%CI] 1.1 – 2.4 per 100 patient years, and the progression rate to death was 0.7 (95%CI 0.3 – 1.3) per 100 patient years.12 These clinical outcomes are equivalent or better than those reported in cohorts from developed countries. For example, progression rates to both AIDS and death in the EuroSIDA cohort in the late HAART era (1998 onwards) was 2.6 per 100 patient years.13

A clinical research network in a resource-limited setting can inform local policy development, and provide evidence for the rational use of drugs in a local population setting.

One of the most important reasons for conducting clinical studies in
a local setting is the important information which can be derived and used to individualize treatments and influence policy and treatment guidelines. Thailand was one of the first resource limited countries to implement a national ART program. Dual combination ART was initially introduced through the Ministry of Public Health (MOPH) in 1995, and since December 2000, the MOPH has recommended highly active antiretroviral therapy (HAART) as the standard of care. Studies at HIV-NAT on double versus triple nucleosides provided important information to the MOPH for making this policy change.14, 15

An analysis of disease progression in our cohort demonstrated the risk of disease progression in subjects with baseline CD4 count 200 – 350 cells/mm³ was not significantly different to those with baseline CD4 count greater than 350 cells/mm³. In contrast, those with baseline CD4 had a risk of disease progression 3.7 (95% CI 1.3 – 10.2) times higher than those with higher CD4 cell counts.12 These results provide support for the WHO recommendations on initiating ARV therapy in resource limited settings, which are also consistent with Thai National Treatment guidelines.16, 17

Clinical studies currently in progress continue to provide important information about delivering HAART in under specific local conditions. For example, the most common event which defines progression to AIDS in our patient cohort is Tuberculosis.12 Patients presenting with low CD4 count who are co-infected with TB present a difficult treatment dilemma as immune reconstitution syndrome can occur after staring ARV.18 This kind of treatment dilemma is rarely encountered in the West, so that the HIV/TB co-infection trials now in progress (see www.hivnat.org/current.html), provides an evidence base for the optimum way to care for these patients. The results of this study will be relevant for all RLS in Asia and Africa with high HIV prevalence rates, where tuberculosis is also endemic.12, 19 There is a similar scenario with Hepatitis B co-infection which exists with high prevalence in Thailand and many other Asian countries. HIV-NAT trials 022 and 023 are exploring new strategies for the treatment of Hepatitis B and HIV co-infected patients.

Rational use of any drug requires the right dose to be given to the patient so that efficacy is maximized, but toxicity is minimized. Many early phase dose-finding clinical trials that result in standard dose formulations being developed and licensed are conducted in the West. As such, the recommended doses may not be appropriate for patients in Asia who have lower body mass index and different drug metabolizing genotypes and phenotypes. Clinical studies conducted at HIV-NAT have identified that doses recommended for subjects in the West lead to toxicity when given to Thai patients. For example, Thai patients developed severe renal toxicity when started on Indinavir 800mg bid boosted with 100mg bid of ritonavir.20, 21 However, further pharmacokinetic and clinical studies demonstrated that dose reductions could maintain viral suppression whilst reducing renal toxicity.22 As another example, we have recently compared the effects of different protease containing HAART regimens on dyslipidemia in Thai patients.23
In addition to providing an evidence base for treatment, HIV-NAT has built capacity in Thailand and other Asian countries. HIV-NAT has provided training for health professionals in the treatment and management of patients with HIV infection though training workshops on good clinical practice, HIV clinical management and good laboratory practice for Thai healthcare workers and those from neighboring countries. Also, a 3 day conference, the ‘Bangkok Symposium on HIV Medicine’ has been held yearly since 1998, and this provides updates to regional healthcare workers on a broad range of HIV-management issues (see www.hivnat.org).

In addition, the pharmacokinetic laboratory at HIV-NAT has assisted the Thai Government Pharmaceutical Organization (GPO) in bioequivalence tests necessary for licensing generic ART which are used in National Treatment Programs. Strategies can be developed in RLS to maintain ART for clinical trial participants after the trials have ended.

HIV-NAT has successfully maintained ART supplies to trial participants at the conclusion of their studies. Initially this was done by enrolling patients in ‘rollover’ studies. In 2000, sponsors were required to provide drugs for a minimum of two years after trial completion. In 2001, the HIV-NAT drug fund was created to subsidize continuation of ART for patients unable to afford their own drugs after completing a trial. Under this scheme, a patient co-payment system operates on a sliding scale.

Conclusion

Cooperation between academic researchers, clinicians, laboratory technical staff, nurses and pharmacists in developed and less developed countries, has made HIV-NAT a successful clinical research network in Thailand. This network has provided access to ART and appropriate clinical care, with low loss to follow-up. As a consequence, there have been low rates of disease progression amongst HIV-NAT patients. HIV-NAT has also built capacity and expertise in Thailand and neighboring countries, and encouraged other Thai institutions to conduct HIV research. The individual outcomes of HIV-NAT patients are a result of this infrastructure, and demonstrate that developed country standard ART success can be achieved in resource-limited countries with appropriate assistance and development of local capacity.

Evidence based health care and the rational use of medicines dictates that patients receive medications
appropriate to their individual needs, at the lowest cost to them and their community. HIV-NAT provides a model for delivering this standard of care in resource-limited settings. HIV-NAT also demonstrates that excellent clinical outcomes can be achieved in less developed country settings, provided adequate funding and resources are made available.

References


