EXPERT ASSISTANCE FOR RESEARCH
IN THE FIELD OF

Prevention and treatment of HIV/non-HIV infections
and virus-associated cancers in Thailand

UNDER AN AGREEMENT FROM
Thailand International Development Cooperation Agency (TICA)

Final Report
2011 – 2016

REQUESTING AGENCY
Faculty of Associated Medical Sciences
Chiang Mai University - Ministry of Education, Thailand

SOURCE OF ASSISTANCE
Institut de Recherche pour le Développement (IRD), France
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1. EXECUTIVE SUMMARY

Prevention and treatment of HIV/non-HIV infections and virus-associated cancers in Thailand

The 2011-2016 AMS-PHPT TICA project is a Research, Capacity building and Education Program in Clinical epidemiology coordinated by the Faculty of Associated Medical Sciences, Chiang Mai University, which involves the Medical Technology, Occupational and Physical Therapy and the Radiologic Technology Departments. It builds upon the partnership established in 2001 with the PHPT research unit within the Institut de Recherche pour le Développement (IRD), a government multidisciplinary research institute in France.

This project planned to expand upon the achievements of the previous 2006-2011 TICA collaborative program between Thailand (Chiang Mai University, Mahidol University and the Thai Ministry of Public Health), the French Institut de Recherche pour le Développement, and Harvard University, resulting in the successful completion of several nationwide clinical trials, pathogenesis and socio-economic studies.

New challenges had emerged:

The long term follow-up of HIV infected patients has revealed that complications related to HIV and/or drug side effects can still occur after years of successful treatment.

While HIV treatment is now widely available in public hospitals in Thailand, only about half of HIV infected people are on antiretroviral treatment, a large proportion of whom ignore their HIV status, missing opportunities for a better control of the epidemic.

With the successes in the control and management of the AIDS epidemic, the relative importance of other diseases has increased. Some infectious diseases, whether or not associated with HIV, can cause cancers, such as hepatitis B or C chronic infections (liver cancers), human papilloma virus infection (cervical cancers).

Another concern is the high prevalence of tuberculosis in Thailand, which remains on the list of 22 High Tuberculosis Burden countries.

Research in these areas can benefit from the successful approach that has been developed to address the HIV epidemic.

Through this collaboration, the Faculty of AMS is strengthening its capacity to contribute to clinical research, notably in the field of infectious diseases of public health importance in South East Asia, and its master and PhD programs.

The two main objectives of the current collaboration project (2011-2016) were:

1. To strengthen the regional clinical research capacity through the development of a clinical research platform within the Faculty of AMS.

The 2011-2016 program aims at strengthening and broadening the clinical research capacity of the Faculty of Associated Sciences and other CMU faculties to address further the present and upcoming biomedical research agenda. This is being done primarily through joint research activities, scientific meetings, seminars, and formal academic courses. Training activities focus on protocol development, study design, grant writing, ethical, management of regulatory aspects of research, implementation issues, good clinical and laboratory practices. The linkage of the platform with international clinical research networks provides additional support and foster essential scientific exchanges.

The AMS-PHPT collaborative program provides trainings for health care professionals—physicians, nurses, pharmacists, medical technologists at collaborating hospitals and from abroad—as well as for people living with HIV/AIDS and/or chronic viral hepatitis and community representatives. This complements the Chiang Mai University higher education programs offered to neighboring countries in the Greater Mekong Sub-region. The project also provides opportunities for undergraduate,
graduate and PhD students in medical sciences, public health, and social/economic sciences, to be trained within the research collaboration, to receive local or international support.

2. Design and test strategies to:

2.1 Prevent HIV transmission in high risk situations
- Interventions to prevent HIV transmission in specific high risk situations and manage HIV in vulnerable populations (children, adolescents and pregnant women).

2.2. Study and manage long term complications of HIV infection and antiretroviral treatment
- Long term complications of HIV and antiretroviral treatment, including cancers, cardiovascular, kidney, bone, liver, neuro-cognitive and metabolic

2.3. Design and test strategies to manage non-HIV infections and virus-associated cancers.
- Interventions to prevent and treat non-HIV virus infections: prevention of hepatitis B virus (HBV) perinatal transmission in HBV mono-infected women, treatment of hepatitis C virus infection in HIV-co-infected patients.
- Detection, prevention and treatment of cancers associated with Hepatitis B or C viruses, and Human Papilloma Virus in HIV infected women.

Other Thai and international partners are involved in projects and trainings developed under this program, including other Chiang Mai University faculties; the faculty of Science at Kasetsart University; the Faculties of Medicine at Ramathibodi Hospital and Siriraj Hospital; NIH funded research networks (International Maternal Pediatric, Adolescent AIDS Clinical Trials network), Harvard T.H. Chan School of Public Health and Harvard School of Medicine in Boston, University of Washington in Seattle, in the US; and the Institut National d’Etudes Démographiques (INED), Paris René Descartes, Paris-Sud Universities, Lyon University, François Rabelais University in Tours, and Infectious Diseases research networks in Europe (PENTA, EUROCoord).

In summary, the ongoing activities of this 5-year project (July 2011–June 2016) contribute to the strengthening of the multi-disciplinary clinical research platform based at the Faculty of AMS at Chiang Mai University. Thai and international partners are working to reinforce the regional and national capacity and infrastructure for clinical, laboratory and operational research addressing critical public health issues related to infectious diseases and non-infectious disease of public health importance in Thailand and in neighboring countries. They are providing critical data to policy makers from the Ministry of Public Health and the international scientific community.
2. STRENGTHENING REGIONAL CLINICAL RESEARCH CAPACITY

An ongoing mission of the Faculty of Associated Sciences is to establish a clinical research platform which supports basic, clinical and translational, and socio-behavioral research to improve patient care and health. This research integrates all aspects from screening, prevention, diagnosis, to treatment. To build/establish a functional and sustainable platform, the Faculty of Associated Sciences started using as a model the PHPT Clinical Research Platform which has gained experience over the last 10 years and has demonstrated its expertise in completing three large nationwide phase III clinical trials.

This research platform has facilitated research involving human subjects, human samples, data derived from humans and research using biological or non-biological products which are tested on humans while ensuring that research on humans is conducted according to ethics guideline outlined by the Helsinki Declaration.

The clinical research platform comprises three main components:

- The capacity and infrastructure to conduct high quality clinical research, including trials, in domains other than HIV and its co-infections;
- A multidisciplinary technological platform constituted by the laboratory, with its microbiology, immunology, biochemistry and pharmacology components
- A multidisciplinary methodological platform, involved from the design to the analysis of preclinical and clinical studies, and supporting all angles of biomedical research, from pathophysiology to public health decision support and socio-economic assessment.

The clinical research organization developed to conduct the PHPT clinical trial has grown with the breadth of the studies performed and is composed today of an administrative support Department (accounting, secretariat, translation, office for regulatory issues and training), a Clinical monitoring Unit, a Data Center (tracking, data processing/management; quality assurance; document archiving), the HIV dedicated laboratory (sample management, processing and storage), a study drugs management unit (reception, storage and shipment of study drugs and supplies), and a Community Advisory Board. Ad hoc committees are created for specific studies such as Data and Safety Monitoring Boards and Resistance Committees, Endpoint Adjudication working groups.

The techniques established at AMS included DNA PCR diagnosis, Viral load, HIV sequencing, HIV typing, Pharmacokinetics capacity, as well as a Quality management system to organize the relationships between all departments necessary for the management of clinical research studies. Novel and powerful technologies (functional genomics, proteomics, bioinformatics and functional imaging) have provided new opportunities to improve diagnostic methods and treatment of numerous human diseases. However, implementation of these new discoveries in a clinical setting is still lagging emphasizing the need for a comprehensive platform for translational research, in particular on infectious diseases.

As a large number of clinical, epidemiological, pharmacological and genetic data are accumulating over time on HIV-infected patients, researchers attempt to understand better the complexity of HIV pathogenesis and the components of disease progression that are patients specific. As a consequence, the upcoming research efforts in HIV prevention and treatment are less and less focused on HIV-specific immunological or virological issues. Instead, they must now encompass the whole complexity from genomics to metabolism, to age-associated mechanisms of cancer.

Specific innovative or advanced methodologies are hence needed to identify and extract relevant information from complex and large databases, and to efficiently design future studies. While conventional methods have been and still need to be used to ascertain basic relationships between cause and effect, advanced biostatistics and computer-based tools are increasingly required to account for the complexity of the available data.

Based on what has been learned during the last 15 years in the fight against HIV infection, it appears that some problems related to these infections could be addressed with similar strategies. For example, perinatal transmission of hepatitis B or cytomegalovirus may be prevented using drugs during pregnancy.
This clinical research platform specifically focused on the inter-disciplinary challenges to be addressed in the HIV or non-HIV research program. More specifically, priority objectives of the methodological capacity building target the techniques required to:

- Identify and characterize HIV resistance mutation pathways with respect to ARV drugs: this allowed more specific monitoring and may delay the emergence of drug resistance, hence reducing the need for second-line treatments especially in countries where new, expensive drugs are not yet available. For this purpose, bioinformatics and pathways analysis methods were implemented to identify patterns from large multivariate mutations data;

- Characterize and quantify the inter-individual variability of ARV drugs pharmacokinetics, and toxico-dynamics, in relation to the genetic background of patients: to allow safer and more specific ARV dosing for the Thai population and better anticipation of toxicity and efficacy of new ARV drugs introduced into Thailand. For this purpose, physiologically-based modeling have been used to predict distribution and metabolism of drugs, accounting e.g. for enzyme polymorphisms and pharmacokinetics specific to genetic background of Thai subjects, so that treatments are tailored to the Thai population;

- Identify and quantify the inter-dependencies of age-associated events as well as the multivariate factors (e.g. inflammation or immune activation) associated with clinical events in patients on HAART for longer-term monitoring and treatment of HIV. For this purpose, statistical multivariate nonlinear modeling were used to address such long-term longitudinal data and specific inference techniques such as Bayesian statistics applied to fit such advanced model to the data;

- Integrate genetic, in vitro, clinical and epidemiological data to optimize evidence-based design of further studies, where classical randomized trials approach cannot be implemented. In particular, new studies investigating the timing of perinatal transmission of Hepatitis B virus or Cytomegalovirus have been designed using advanced methodologies allowing optimal use of available information to minimize study size or duration. Similarly, a new study to investigate relationships between HPV, HIV and risk of cervical cancers has been designed based on accumulated data and knowledge on HPV/HIV and cervical cancer in Thai women.

Collaborators of this platform included long-time experienced researchers of AMS and PHPT projects, such as the French Institute of Demographics (INED), Paris 5 and Paris 11 Universities, The Bioinformatics Research Lab and Department of Statistics, Faculty of Science, Chiang Mai University and the Department of Statistics, Faculty of Science, Kasetsart University. Such a platform has operated cross-functionally in many of the clinical projects which results are reported in section 3 as many of the techniques to be implemented were similar. Aside from the specific support to each project, the overall aim was to develop sustainable internal capacities in the areas of clinical trial methodologies and logistics, biostatistics, bioinformatics, pharmacokinetic modeling, system biology tools and health economics that could address the upcoming challenges of biomedical research. Specific techniques to be developed and/or maintained include: design optimization, design evaluation, systematic review and meta-analysis, protocol writing and grant submission, diagnostic test development and analysis, data management, statistical modeling, genetic and high-throughput data analysis, data mining, quantitative epidemiology and risk assessment, drug effectiveness, image analysis, physiologically based pharmacokinetic (PBPK) modeling, predictive toxicology, pharmacokinetics/pharmacodynamics (PK/PD) and dose-response modeling, Monte Carlo simulations, decision analysis, cost-effectiveness analysis.

It should be highlighted that a sustainable integration of the clinical research platform within Chiang Mai University can only be achieved through:

1. High-level education program promoting and initiating long-term partnerships within Thailand and with international teams;

2. Capacity building and maintenance of high standard research methodology capacities to provide ad hoc consulting/expertise service;

3. Full integration of methodological expert within research projects

This platform has fostered collaboration between researchers with similar research interest yet different professional backgrounds (interdisciplinary research collaborations) to produce innovations.
or interventions which can improve patient care or prevent certain diseases. It also created an educative environment linking education to research within Chiang Mai University and other national or international research universities. Importantly, the research findings have been disseminated to improve policies and practices (information and knowledge will be spread through internet and regular meetings and symposia). Within this platform, have been provided training on clinical research, human subject protection, Good Clinical Practice, ISO Quality systems and procedures as well as on methods to develop ad hoc study protocols.

3. RESULTS OF THE STUDIES

3.1 Preventing mother to child transmission of infectious diseases

3.1.1 PHPT-5 clinical trial: avoiding the risk of HIV resistance to nevirapine

PHPT-5 First phase


Justification

Maternal and infant single-dose nevirapine (sdNVP) in addition to ZDV prophylaxis from 28 weeks of pregnancy decreases HIV perinatal transmission in non-breastfed infants to 1-2% but is associated with selection of NVP resistance mutations. We hypothesized that giving NVP only to the infant, or adding maternal lopinavir/ritonavir (LPV/r) to antepartum ZDV without any NVP, would be as efficacious, and safe as the standard regimen and would avoid the selection of resistance mutations in the child and/or the mother.

Methods

This is a randomized, partially blinded, non-inferiority clinical trial comparing the efficacy and safety of the following three regimens:

- **Regimen A**: a single dose of nevirapine in infants immediately after birth without maternal nevirapine, in addition to standard zidovudine prophylaxis starting from 28 weeks gestation
- **Regimen B**: ritonavir boosted lopinavir plus zidovudine from 28 weeks gestation without infant nevirapine.
- **Regimen C** (reference regimen) : recommended by the WHO and Thai guidelines, zidovudine from 28 weeks gestation plus NVP given to both mother and infants (single dose for mothers, and two doses for neonates), with one week of zidovudine+lamivudine post-partum to mothers to prevent emergence of NVP resistance mutation.

This trial enrolled HIV-infected pregnant women who did not meet the criteria to start antiretroviral therapy for their own health (CD4 threshold increased from 250 to 350 cells/mm3 during the study).
Infants received zidovudine for one week and were formula fed. Women and children are followed for 2 years after delivery. This trial was designed for a total 2097 women-infant pairs in 43 hospital sites throughout Thailand.

**Status & Main results**

On October 1st, 2010, enrolment was suspended and data unblinded upon the Data Safety Monitoring Board recommendations following the modification of the Thai prevention of mother to child transmission of HIV guidelines that recommended the use of HAART in all HIV infected pregnant women regardless of their CD4 counts.

As of October 1st, 2010, **435 pregnant women** had been enrolled and the overall HIV transmission rate was 2.2% (95%CI: 0.7% to 3.6%). There were no significant differences between the three arms in terms of transmission and adverse pregnancy outcomes but most transmissions occurred in women with short antepartum antiretroviral treatment duration, regardless of the intervention arm. Factors independently associated with transmission were less than 8 weeks of antiretroviral prophylaxis and a high viral load at baseline.

**Collaborators**

- Dr. Somsak Pattarakulwanich, MoPH
- Dr. Nipunporn Voramongkol, MoPH
- Dr. Siripon Kanshana, MoPH
- Prof. Dr. Suporn Koetsawang, Mahidol University
- Dr. Virat Klinbuayam, MoPH

**Funding:** NIH - NICHD (USA), R01 HD052461 and R01 HD056953.

**Key publications**


**PHPT-5 Second phase**

Perinatal antiretroviral intensification for the prevention of mother-to-child transmission of HIV in Thai women having received less than 8 weeks of HAART during pregnancy (NCT01511237).

**Justification**

As demonstrated in the PHPT-5 1st phase study, women who start antiretroviral treatment late during pregnancy have at high risk of transmission of HIV to their babies. The primary objective of this trial is to evaluate the efficacy of maternal and infant perinatal antiretroviral prophylaxis intensification for the prevention of mother-to-child intrapartum transmission of HIV-1 in women receiving less than 8 weeks of antiretroviral prophylaxis during pregnancy. Secondary Objectives are (1) To compare the safety of infant antiretroviral intensification, with that of the standard prophylaxis, taking into account the maternal treatment received; (2) To estimate overall risk and timing of transmission of HIV-1 in relation with maternal and infant prophylaxis; (3) To determine the viral load dynamics during pregnancy in relation to LPV/r+ZDV+3TC duration of treatment and drug levels.
Methods

The study is designed as a multicenter, phase III, single-arm trial.

The standard of care in Thailand is defined as:

- Maternal antiretroviral treatment: ZDV 300 mg, 3TC 150mg and LPV/r 400/100 twice a day starting as soon possible after 14 weeks of pregnancy + ZDV 300 mg every 3 hours during labor; this treatment may be continued, stopped or modified after delivery upon the recommendation of the internist.

- Newborn: ZDV 4 mg/kg every 12 hours for 4 weeks (ZDV dosing adjusted for premature infants).

*Perinatal antiretroviral intensification* (study treatment) is defined as the addition to the standard of care for mothers and infants of maternal single dose (sd) NVP at onset of labor and 2 weeks infant ZDV+3TC+NVP followed by 2 weeks ZDV+3TC in addition to standard of care (HAART in mothers during pregnancy and ZDV prophylaxis in infants). Note: Women who will have received single dose nevirapine will continue HAART for 4 weeks post-partum.

The trial was initially planned to enroll 118 HIV-infected women and their infants in the intervention group if no intrapartum transmission would occur.

**Status & Main results**

As of 12 May, 2014, **379 pregnant women** had been enrolled, 329 delivered, including 88 in the intervention group. As a consequence of the Royal Thai Government' new PMTCT guidelines to provide all pregnant women with HAART early during pregnancy, enrolment has been slower than expected. In terms of perinatal transmission of HIV, there were 3 *in-utero* transmission in the intervention group, and 2 *intra-partum* transmission in the observation group. No *intrapartum* transmission had been observed in the intervention group.

On May 12, 2014 the DSMB recommended to the study team to stop enrolment and proceed to the final analysis and reporting of the study results as soon as possible.

**Collaborators**

- Dr. Somsak Pattarakulwanich, MoPH
- Dr. Nipunporn Voramongkol, MoPH
- Dr. Siripon Kanshana, MoPH
- Prof. Dr. Suporn Koetsawang, Mahidol University
- Dr. Virat Klinbuayam, MoPH

**Funding:** NIH, NICHD (USA), R01 HD052461 and R01 HD056953.
Key publications:

- Efficacy and safety results were presented at the 8th International AIDS Conference on HIV Pathogenesis, Treatment and Prevention, July 2015.

This model was developed by a Thai PhD student, Patumrat Sripan, under the direction of Marc Lallemant to investigate the efficacy of different drug combinations for the prevention of mother-to-child transmission, and published in May 2015.

3.1.2 Antiretroviral treatment after delivery (IMPAACT studies)

Evaluation of antiretroviral treatment in mothers with high levels of CD4: IMPAACT 1077HS (PROMISE study)

Background

Pregnant women infected with HIV start antiretroviral treatment for the prevention of mother-to-child transmission of HIV and usually stop this treatment after delivery if they do not need it for their own health, i.e. if their CD4 level is above 350 cells/mm3.

Objectives

The objective of the IMPAACT 1077HS study is to assess whether women who do not need HIV treatment for their own health (CD4 count over 400 cells/mm3) should continue therapy or not after delivery.

Methods

A total of 2,000 mothers will be randomized in the US, South America, Africa, and Thailand and followed up to 5 years in this multinational study. The primary endpoint is death, AIDS-defining illness, or serious non-AIDS-defining cardiovascular, renal, and hepatic events. Several sub-studies are planned, in particular on inflammation and activation markers.
Progress
The 5 hospital sites affiliated with the PHPT network have been very active in this study. In total, 147 pregnant women were enrolled and 133 are still on follow up. The study is expected to be completed in September 2016.

Funding: National Institutes of Health / NIAID, through the IMPAACT network.

3.1.3 iTAP clinical trial: Prevention of hepatitis B virus perinatal transmission

Background
Hepatitis B is an incurable infection - though some antiviral drugs, which inhibit viral replication, decrease the risk of its main long term two complications: cirrhosis and liver cancer. Before the incorporation of hepatitis B virus (HBV) vaccine in the Expanded Programs for Immunization, perinatal transmission was the main route of transmission of HBV in South East Asia. At least 90% of early fetal/infant infections result in HBV chronic infection (detected by the presence of the HBV 's' antigen or HBsAg), responsible for liver disease and cancer. Immunization using specific vaccine starting after birth and immunoglobulins (HB Ig) can decrease mother to child transmission of HBV by 95%. However, despite passive-active immunization, infants born to mothers with high HBV replication have a 10% risk of infection. To date, no other methods have been shown effective to prevent perinatal transmission from mothers with high viral replication and safe for both mothers and infants. An effective and safe method to prevent all perinatal transmission of HBV would contribute to worldwide elimination of HBV infection.

Objectives
To assess the efficacy and tolerance of a maternal short antiviral drug regimen to prevent perinatal transmission of HBV.

Methods
Pregnant women with a positive hepatitis B 'e' antigen test (indicative of high viral replication) and no need for antiviral treatment according to current guidelines, are randomized to receive either tenofovir disoproxil fumarate or placebo from 28 weeks’ gestation and two-month post-partum. All newborns receive passive-active immunization. As discontinuation of antiviral treatment has been shown to trigger a viral replication rebound and acute hepatic inflammation (shown by high levels of alanine aminotransferase or ALT), the safety of maternal antiviral discontinuation is carefully assessed over one year after delivery. Infants are also followed for one year and HBV infection status is ascertained using both HBsAg test and HBV DNA load.

Figure: Overview of the randomized trial design with 12-month follow-up
Progress

2513 women have been screened for the study in 17 clinical research sites. The enrollment was completed in August 2015, with 331 women randomized in the clinical trial. The Data and Safety Monitoring Board (DSMB) met in February 2014 and February 2015 for safety reviews and in July 2015 for the review of the interim analysis and recommended each time to continue the study without changes.

Funding: National Institutes of Health (NIH), Center for Diseases Control and Prevention (CDC), US; and Institut de recherche pour le développement.

3.1.4 Prevention of congenital cytomegalovirus infection

⇒ The Ability of Maternal Nelfinavir Treatment to Prevent Congenital Cytomegalovirus Infection: A Pilot Study Nested within PACTG 316, P1025 and KiBS.

This is a collaborative project with Lisa Frenkel, University of Washington, USA.

Background: Congenital infection with cytomegalovirus (CMV) is the most common congenital viral infection affecting 0.1 to 2.0% of all live births worldwide. It is an important cause of mental retardation and developmental disability, including hearing loss. Higher rates of congenital CMV infection have been systematically found in HIV-infected infants. Currently, there are no simple methods to prevent congenital CMV infection.

Objective: To assess whether antiretrovirals, active in vitro against both HIV and CMV, given to HIV infected pregnant women can reduce the rate of congenital CMV infection.

Methods: Plasma and PBMC specimens collected were tested using the standard real-time CMV PCR assay at the University of Washington Molecular Virology Laboratory.

Outcome: A total of 1,255 samples were tested in this retrospective study (314 from nelfinavir-exposed newborns and 941 controls). The overall prevalence of congenital CMV infection in the infants was 2.2%, and was not associated with maternal NFV use.

Conclusion: The risk of congenital cytomegalovirus infection among HIV-exposed uninfected infants was not decreased by maternal nelfinavir use during pregnancy in this retrospective study.

Funding: IMPAACT- NIAID


3.2 Optimizing drug dosing and formulations for Thai patients

The pharmacokinetics of some drugs vary in special populations, such as pregnant women, infants, children, and this may affect their efficacy and/or safety. The AMS-IRD pharmacology laboratory has been addressing these issues though several studies, including the following ones.

3.2.1 Pharmacokinetic studies in pregnant women

The Thai Antiretroviral Treatment guidelines recommend HAART for all pregnant women. However the optimal dose of antiretroviral drugs needed to treat HIV infection in pregnant women and to protect babies from HIV infection is not known for all antiretroviral drugs. Furthermore appropriate dosing for pregnant woman is critical to the health of both mother and fetus. Overdosing may lead to maternal adverse events and increased risk of fetal toxicity. Under dosing may lead to inadequate virologic control, increased risk of developing drug resistance mutations and a higher rate of perinatal HIV transmission.

The objective of the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1026s study is to describe the pharmacokinetic parameters during pregnancy of selected ARV currently used in the clinical care of pregnant HIV-infected women, and to determine if therapeutic dosing regimens of these antiretroviral drugs produce adequate drug exposure during pregnancy compared to a) historical data from non-pregnant adults and b) the same women in the study cohorts during the postpartum period [ClinicalTrials.gov Identifier: NCT00042289].
**Efavirenz Pharmacokinetics during the Third Trimester of Pregnancy and Postpartum**

The impact of pregnancy on efavirenz pharmacokinetics is unknown. The P1026s study included a cohort of HIV-infected pregnant women receiving 600 mg efavirenz once daily as part of combination antiretroviral therapy. Intensive steady-state 24-hour blood sampling was performed during the third trimester and at 6-12 weeks postpartum. Maternal and umbilical cord blood samples were drawn at delivery. Pharmacokinetics targets were the estimated 10th percentile efavirenz AUC in non-pregnant historical controls (40.0 mcg.hr/mL) and a trough concentration of 1 mcg/mL.

**Outcome:** 25 women (21 Thai and 4 USA) were enrolled during the third trimester: median (range) age was 29.3 (18.9-42.9) years, weight 69.0 (40-130) kg, gestational age 32.9 (30.1-38.7) weeks. Median (range) efavirenz AUC0-24, Cmax and C24h were 55.4 mcg.hr/mL (13.5-220.3), 5.4 mcg/mL (1.9-12.2) and 1.6 mcg/ml (0.23-8.13), respectively. Efavirenz AUC and Cmax did not differ during pregnancy and postpartum but C24h was lower during the third trimester (1.6 vs. 2.1 mcg/mL, p=0.01). During the third trimester, 5 of 25 (20%) women had an efavirenz AUC below the target and 3 of 25 (12%) had a trough concentration below 1 mcg/mL. Efavirenz cord blood/maternal concentration ratio was 0.49 (0.37-0.74). All women had a HIV-1 RNA viral load less than 400 copies/mL at delivery and 19 (76%) had a viral load below 50 copies/mL. One child was perinatally HIV-infected. Three women were exposed to efavirenz throughout the first 6 weeks of pregnancy. EFV was well tolerated and among the 25 infants no congenital anomalies or newborn complications were reported.

**In Summary:** Changes in efavirenz pharmacokinetics during pregnancy compared to postpartum are not sufficiently large enough to warrant a dose adjustment during pregnancy.

**Publications:**
- Cressey TR, Stek A, Capparelli E, Bowonwatanuwong C, Prommas S, Huo Y, Read J, Smith E, Best B, Mirochnick M, for the IMPAACT P1026s Efavirenz Pharmacokinetics During the 3rd Trimester of Pregnancy and Postpartum. 18th Conference on Retroviruses and Opportunistic Infections, February 27-March 2, 2011, Boston, USA. Poster #754

**Figure:** Median (± interquartile range) concentration versus time curves for HIV-infected pregnant women using 600 mg, once daily during the third trimester and postpartum. Dashed line represents the typical 50th percentile concentrations in non-pregnant historical patients.

**Reduced indinavir exposure during pregnancy**

Data on the pharmacokinetics and safety of indinavir boosted with ritonavir (IDV/r) during the second and third trimesters of pregnancy and in the postpartum period are limited in Thai women. The P1026s study included a cohort of HIV-infected pregnant women receiving IDV/r 400/100 mg twice
daily during pregnancy through 6-12 weeks postpartum as part of clinical care. Steady-state PK profiles were performed during the second (optional) and third trimesters and at 6-12 weeks postpartum. PK targets were the estimated 10th percentile IDV AUC (12.9 µg.h/mL) in non-pregnant historical Thai adults and a trough concentration of 0.1 µg/mL, the suggested minimum target.

Outcome: 26 pregnant women were enrolled in Thailand; thirteen entered during the second trimester. Median (range) age was 29.8 (18.9-40.8) years and weight 60.5 (50.0-85.0) kg at the third trimester PK visit. The 90% confidence limits for the geometric mean ratio of the indinavir AUC0-12 and Cmax during the second trimester and postpartum (ante/post ratios) were 0.58 (0.49-0.68) and 0.73 (0.59-0.91), respectively; third trimester/postpartum AUC0-12 and Cmax ratios were 0.60 (0.53-0.68) and 0.63 (0.55-0.72), respectively. IDV/r was well tolerated and 21/26 women had a HIV-1 viral load <40 copies/mL at delivery. All twenty-six infants were confirmed HIV negative.

In Summary: IDV exposure during the second and third trimesters was significantly reduced compared to postpartum and ~30% of women fail to achieve a target trough concentration. Increasing the dose of IDV/r during pregnancy to 600/100 mg twice daily may be preferable to ensure adequate drug concentrations.

Publications


Pharmacokinetics of an increased atazanavir dose with and without tenofovir during the third trimester of pregnancy

Reduced atazanavir exposure has been shown during pregnancy with standard atazanavir/ritonavir (ATV/r) dosing. We studied an increased dose during the third trimester of pregnancy. The P1026s study included 2 cohorts (with or without tenofovir) receiving atazanavir/ritonavir 300/100 mg once daily during the second trimester, 400/100 mg during the third trimester, and 300/100 mg postpartum (PP). Intensive steady-state 24-hour pharmacokinetic profiles were performed. Pharmacokinetic targets were the 10th percentile atazanavir area under the concentration versus time curve (AUC) (29.4 mcg.hr/mL) in non-pregnant adults on standard dose and 0.15 mcg/mL, minimum trough concentration.

Outcome: Atazanavir pharmacokinetic data were available for 37 women without tenofovir, 35 with tenofovir; median (range) pharmacokinetic parameters are presented for second trimester, third trimester, and PP and number who met target/total.

Atazanavir without tenofovir: AUC 30.5 (9.19-93.8), 45.7 (11-88.3), and 48.8 (9.9-112.2) µg·hr·mL, and 8/14, 29/37, and 27/34 met target. C24 h was 0.49 (0.09-4.09), 0.71 (0.14-2.09), and 0.90 (0.05-2.73) µg/mL; 13/14, 36/37, and 29/34 met target.

Atazanavir with tenofovir: AUC 26.2 (6.8-60.9) (P < 0.05 compared with PP), 37.7 (0.72-88.2) (P < 0.05 compared with PP), and 58.6 (6-149) µg·hr·mL, and 7/17, 23/32, and 27/29 met target. C24 h was 0.44 (0.12-1.06) (P < 0.05 compared with PP), 0.57 (0.02-2.06) (P < 0.05 compared with PP), and 1.26 (0.09-5.43) µg/mL; 7/17, 23/32, and 27/29 met target. Atazanavir/ritonavir was well tolerated with no unanticipated adverse events.

In Summary: Atazanavir/ritonavir increased to 400/100 mg provides adequate atazanavir exposure during the third trimester and should be considered during the second trimester.

Publications

Impact of Body Weight and Missed Doses on Lopinavir Concentrations with Standard and Increased Lopinavir/Ritonavir Doses during Late Pregnancy

The objective was to assess the influence of body weight and missed doses on lopinavir pharmacokinetics with standard and increased doses of lopinavir/ritonavir tablets during late pregnancy. Lopinavir concentration data during the third trimester of pregnancy were pooled from the PHPT-5 clinical trial in Thailand (NCT00409591) and the P1026s trial in the United States (NCT00042289). Lopinavir population parameters were estimated using non-linear mixed effects regression models. Monte Carlo simulations were performed to estimate the probability of achieving target lopinavir trough concentrations (>1.0 µg/mL) with standard and increased doses of lopinavir/ritonavir during pregnancy.

Outcome. Data from 154 HIV-infected pregnant women (123 Thai and 31 USA) receiving either 400/100 mg (standard) or 650/150 mg (increased) twice daily had lopinavir plasma concentration were included. Median (range) age was 28 years (18-43), weight 62 kg (45-123) and gestational age 33 (29 to 38) weeks. Body weight influenced lopinavir oral clearance (CL/F) and volume of distribution (Vd/F). Population estimates of lopinavir CL/F and Vd/F were 6.18 L/h/70kg and 58.6 L/70kg, respectively. Based on simulations, the highest risk of sub-therapeutic trough concentrations was for women weighing >100 kg using the standard dose, approximately 10%, while the risk was <5% with the 600/150 mg dose for women 40-130 kg. After a missed dose, 52% of women have lopinavir concentrations below target prior to the next dose with the standard dose compared to 36% with the increased doses.

In Summary: Standard dosing provides adequate lopinavir trough concentrations for the majority of pregnant women but increased doses may be preferable for women weighing >100 kg, history of lopinavir/ritonavir use and/or adherence issues.

Publications


3.2.2 Pharmacokinetic studies in children

Antiretroviral therapy (ART) has dramatically improved the prognosis for HIV-infected children transforming a devastating, rapidly progressive lethal condition into a chronic disease. However, treatment of children and adolescents is challenging for several reasons. Adapting the correct antiretroviral dose and formulations as a child grows while maintaining efficacy and minimizing toxicity or problems of medication adherence is critical in particular for infants and children who rely on caregivers for medication administration, and for adolescents undergoing the transition to adulthood.

New treatment strategies which promote adherence, minimize development of resistance and reduce long-term drug exposure while improving quality of life are required for young people 'burning out' on daily ART regimens. Approaches to achieve this include: (i) simplification of therapy (i.e. minimizing the number of pills or swapping from twice to once-daily dosing), (ii) treatment interruptions (not currently advocated) and (iii) very short treatment interruptions (particularly at inconvenient times for taking medication such as weekends).

The following studies were performed in response to these challenges:

- 'Paediatric European Network for Treatment of AIDS' (PENTA)-18/KONCERT Trial
Lopinavir/ritonavir (Kaletra) 200/50 mg tablets and 100/25 mg tablets, to be taken twice daily, are approved for paediatric use. A once-daily dosing schedule would be more convenient in young children and adolescents. The objective of the study is to compare this new dosing schedule with the currently approved schedule.

The KONCERT trial was aimed at assessing the pharmacokinetics, safety and efficacy of lopinavir/ritonavir tablets (dosed by weight) twice-daily (BID) versus once-daily (QD) lopinavir/ritonavir as part of combination antiretroviral therapy in HIV-1 infected children.

It was a randomized, non-inferiority trial in Europe, Thailand, Argentina and Brazil. Children (<18 yrs, >15kg) on LPV/r-containing ART with HIV-RNA (VL) < 50 copies/mL for > 24 weeks were randomized to continue LPV/r BID or switch to QD dosing, according to FDA approved body weight-based dosing. Children were followed for minimum 48 weeks, visits at weeks 0, 4, 8, 12 then 12 weekly. The primary outcome was the percentage with confirmed VL>50 c/mL by 48 weeks, estimated using the Kaplan-Meier method (12% non-inferiority margin). 26 children (on LPV/r 100/25mg pediatric tablets) in the QD arm had LPV/r pharmacokinetic (PK) measurements at weeks 0 (BID) and 4 (QD). Within-subject ratios for QD versus BID of AUC0-24, Cmax and Cmin were calculated. PK analyses were per-protocol, all others intention-to-treat.

**Outcome. 173 children** were randomized to QD (86) or BID (87): 46% male, median age 11 (IQR 9-14) years; 25% white, 27% black, 35% Asian; 29% CDC stage C, median time on ART 7.2 years. Median baseline CD4% was 32% (IQR: 27, 36) QD vs 34% (28, 40) BID. Although all children had VL<50c/mL at screening, 12 (14%) QD vs 4 (5%) BID had baseline VL>50 c/mL (IQR: 66, 239). By week 48 (1 QD child lost at week 4), 97% and 98% of time was spent on QD and BID respectively. 12 QD vs 7 BID children had confirmed VL>50 c/mL within 48 weeks; the estimated percentage with VL rebound was 14% QD vs 8% BID: difference 6% (90% CI -2, 14; p=0.2); reducing to 4% (-4, 11) after adjustment for baseline CD4% and VL in a post-hoc analysis.

No child died or had a new CDC C event. Two children (BID) had a major PI mutation at VL rebound (L90M, M46I+V82A); 3 QD vs 2 BID children had M184V, 2 QD vs 2 BID developed TAMs. Changes from baseline to week 48 in CD4%, CD4 count, biochemistry, hematology and lipids were similar between arms, as were the number of children with grade 3/4 AEs (10 QD vs 7 BID, p=0.6). 14 (4%) QD vs 6 (2%) BID children reported missing a dose within 3 days of any clinic visit (p=0.2). For the 26 QD children in the PK sub-study, the geometric mean ratio (GMR) (90% CI) of AUC0-24 was 0.72 (0.61, 0.85) falling outside the 80-125% limits for bioequivalence. GMR for Cmax was 1.13 (0.99, 1.28) and for Cmin was 0.18 (0.11, 0.29).

**In Summary:** Non-inferiority for VL suppression on QD versus BID LPV/r dosing was not demonstrated in this trial and LPV daily drug exposure was lower with QD dosing. Resistance and safety data were similar in both arms. Although the results can be partly explained by chance VL imbalance at baseline, they do not support the routine use of LPV/r QD in children and adolescents.

**Publications**

- PENTA-18 Team. Final results of KONCERT: a randomized non-inferiority trial of QD vs BD LPV/r dosing in children. 21st Conference on Retroviruses and Opportunistic Infections, Boston, USA, 3-6 March 2014, Abstract #LB74; Oral Presentation

**BREATHER, or PENTA 16 trial**

In order to improve adherence in young people, aged 8 to 21 years, this study tested whether it is possible to interrupt antiretroviral treatment during the week-end without reducing its efficacy.
This was a study for patients who achieved complete virological response to first-line antiretroviral treatment for at least 12 months. BREATHER was a randomised, non-inferiority trial in Europe, Thailand, Uganda, Argentina & US. Subjects (>8, ≤24 yrs old) on efavirenz (EFV)-based therapy were randomised to continue daily ART (CT) or change to Short Cycle Therapy (SCT) (5 days on ART; 2 days off). Follow-up was for minimum 48 weeks. The primary analysis was the difference in proportion with VL>50c/ml by 48 weeks between arms.

Outcome: This prospective, open, multi-center, randomized, controlled phase II/III trial started enrollment in March 2011. Subject recruitment closed on June 28, 2013. 199 subjects from 11 countries were randomised; 99 SCT, 100 CT, and followed for median 86 weeks: 53% male, median age 14yrs; 35% 1 African site; 56% black, 19% Asian; 21% Caucasian; 6 SCT vs 7 CT had confirmed VL>50 copies/ml by 48 weeks; difference (90% CI) -1.2% (-7.3, 4.9); 2 SCT vs 4 CT had confirmed VL>400c/ml; difference 2% (-6.2, 2.0). 7 subjects (2 SCT, 5 CT) had major NNRTI mutations at VL failure; 2 (1 SCT, 1 CT) had M184V. No subjects died; there were no significant differences in toxicity between arms. Subjects expressed preference for SCT in a qualitative substudy and in questionnaires pre-trial and at the end of the trial.

Conclusions: Non-inferiority of VL suppression on SCT vs CT was demonstrated, with similar resistance, safety and inflammatory marker profiles. 98% of subjects are participating in a 2-year followup extension of the trial and the results are expected in December 2016.

Publication

- ART with weekends off is non-inferior to continuous ART in young people on EFV+2NRTI. The PENTA 16 (BREATHER) trial team. Conference on Retroviruses and Opportunistic Infections, Seattle, USA. 23-26 February 2015; Oral Presentation [PHPT, Thailand: TR Cressey, S Chalermpantmetagul, R Peongjakta, K Than-in-at, S Chailert, K Seubmongkolchai, S Thammajitsagul, W Sripaoraya, C Kasemrat, A Upra, G Jourdain, M Lallemant, N Ngo-Giang-Huong, S Le Coeur]

IMPAACT P1083

Current recommendations for lopinavir boosted by ritonavir (LPV/r) dosing in infants and children are based on body surface area and questions remain as to whether they provide optimal lopinavir exposure in all age ranges. Instead, the WHO Pediatric Antiretrovirals Working Group (PAWG) has recommended for use in resource-limited settings simplified antiretroviral dosing based on weight bands in order to simplify drug delivery and reduce prescription errors.

IMPAACT P1083 is a phase II/III trial to assess short-term pharmacokinetics (PK), safety, tolerance, and virological effect of LPV/r in HIV-infected infants and children who weigh ≥3 and <25 kg, dosed according to the WHO ARV weight band guidelines. LPV/r was administered as the heat-stable pediatric LPV/r 100/25 mg tablet or the liquid 80/20 mg/mL formulation, and dosed according to the WHO weight band dosing schedule with two NRTIs as background therapy. Intensive 12-hour PK evaluations were performed after 4 weeks of LPV/r therapy; plasma samples were collected at 0, 2, 4, 6, 8 and 12 hours post observed dosing. LPV/r concentrations were measured by HPLC. Non-compartmental PK analyses were performed; the 90% confidence interval of geometric mean (GM) for LPV and RTV AUC was calculated and compared to a target value from studies establishing safety and efficacy of LPV/r. The target GM (range) for LPV AUC<sub>0-12</sub> was 80 (40,160) mcg.h/mL.

Outcome: 45 children enrolled. 43 had intensive PK: 20 (44.4%) male; median (range) age at entry 3.5 (0.3, 12.8) years; CD4% 25 (1, 45); log<sub>10</sub> RNA 5.0 (2.6, 6.8) copies/mL. Twenty-seven (60.0%) subjects used the liquid formulation. The median LPV dose was 313 mg/m2. The geometric mean (range) of LPV parameters were: AUC=107.4 (29.3, 217.7) mcg.hr/mL; Cmin=3.15 (<0.05, 13.77) mcg/mL; Cmax=12.2 (3.84, 23.39) mcg/mL and CL/F (L/hr/m2)=2.74 (0.145, 11.623). AUC was inversely correlated with age (r=-0.42, p<0.01). There were no ≥ grade 3 adverse events deemed related to study treatment. For 39 children with week 24 results available, the mean (SD) change from baseline to week 24 in log<sub>10</sub> copies/mL HIV-1 RNA was -2.1 (1.6), and in CD4% was 4.9% (5.9).

In Summary: LPV/r prescribed according to the WHO weight band dosing regimen in children achieved adequate plasma exposure, higher than seen in adults with soft gel capsules. Despite the higher LPV/r exposure found in these children, the treatment was well tolerated and the preliminary efficacy data were favorable.
Population pharmacokinetics of efavirenz in HIV-1 infected Thai children

Although the pharmacokinetics of efavirenz is quite well described in adults, limited data are available on efavirenz pharmacokinetics in children, especially in the Asian population. This study aimed to develop a population pharmacokinetic model and describe efavirenz concentration-time courses in a large group of Thai children, and to predict exposures with current pediatric dosage recommendations.

**Status:** started in 2012, completed.

**Outcome:** Efavirenz concentration data in 307 plasma samples drawn from 152 children were included in this analysis. Median (range) age was 11 years (1-18), body weight was 25 kg (7-56), and received a median efavirenz dose of 300 mg (200-600). A one-compartment model adequately described the data. The data was best described using a mixture model assuming two groups of children with different efavirenz oral clearance (CL/F) mean estimates. The first group of children (70%) had a mean CL/F of 18.8 L/h while the second group of children (30%) had a lower CL/F of 12.1 L/h. Seventy-one children (47%) had an efavirenz concentration 24 hours post-dose (C24h) below 1.0 mg/L, and all were among the group of children with higher CL/F. Twelve children (8%) had C24h > 4 mg/L, none of them reported adverse events related to efavirenz. Nineteen (45%) of these 42 children had HIV RNA viral load more than 400 copies/mL (p=0.024).

**In summary,** efavirenz clearance was 35% lower in one third of patients, leading to higher efavirenz exposition. A high proportion of Thai children dosed according to the WHO guidelines 2006 achieved efavirenz through concentrations below the recommended minimum concentration. A significantly higher number of children with an efavirenz C24h below 1.0 mg/L had a viral load more than 400 copies/mL.

**Collaborators:**
- Ingsrisawang L: Department of Statistics, Faculty of Science, Kasetsart University, Bangkok
- Urien S, Treluyer JM: Université Paris Descartes, Paris, France; Unité de Recherche Clinique Paris Centre, Assistance Publique Hôpitaux de Paris, France; 5CIC-0901 INSERM & APHP, Paris, France;
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**Funding:** Global Fund to Fight AIDS, Malaria and Tuberculosis; Oxfam GB THAA51; Ministry of Public Health, Thailand; *Institut de Recherche pour le Développement* (IRD), France.

**Key publications.**


**Efavirenz concentrations and probability of virologic failure and adverse effects in HIV-infected**

This project aimed to assess the pharmacokinetics of efavirenz in HIV-infected children and estimate the probability of virologic failure and adverse effects using US-FDA approved weight-band dosing.

**Status:** started in 2011, completed.

**Outcome:** Using 621 plasma efavirenz concentrations from 188 HIV-infected children, efavirenz population pharmacokinetic parameters were estimated using non-linear mixed effects modeling. Children’s median (interquartile range) age was 10 (7.5-12.7) years, weight 23.5 (18.0-34.5) kg, and efavirenz dose 13 (11.4-14.3) mg/kg. Using FDA approved weight band dosing, it was estimated that on average 15% of fast and <1% of slow metabolizers had a C₁₂ < 1.0 mg/L across the weight bands (Figure 1).

In summary, a higher proportion of children with a C₁₂ < 1.0 mg/L had viral replication compared to those with a C₁₂ > 1.0 mg/L, and a lower C₁₂ and C₂₄ were associated with a higher odds of viral replication. Our pharmacokinetic model predicted that approximately 15% of children would have a C₁₂ < 1.0 mg/L when receiving US FDA-approved weight-band dosing (<1% for children with a slow metabolizer phenotype) and these children had a 23% risk of viral replication.
Figure 1: Percentage of children with $C_{12} < 1.0$ mg/L, between 1.0 to 4.0 mg/L and $>4.0$ mg/L as a function of body weight according to US-FDA approved weight-band dosing for (a) fast metabolizers and (b) slow metabolizers. (c) Efavirenz $C_{12}$ concentration as a function of body weight for fast metabolizers and slow metabolizers. (d) Probability of viral replication $>400$ copies/mL as a function of body weight for fast metabolizers and slow metabolizers.

**Funding:** Global Fund to Fight AIDS, Malaria and Tuberculosis; Oxfam GB THAA51; Ministry of Public Health, Thailand; *Institut de Recherche pour le Développement* (IRD), France.

**Publications:**

This work was conducted by Nontiya Homkham, a PhD student in the CMU-IRD research unit, under the supervision of L. Ingsrisawang and G. Jourdain.

### 3.3 Maximizing long term benefits of antiretroviral therapy

#### 3.3.1 Cohort of patients on antiretroviral treatment

**Failure of PI based second line ART in HIV-1 infected children in Thailand**

This study aimed to estimate the rate and identify risk factors of virologic failure in children on protease inhibitor (PI) based second-line antiretroviral therapy (ART) in Thailand.

**Status:** started in 2012, completed.

**Background:** HIV infected children failing second-line antiretroviral therapy (ART) have little or no access to third-line antiretroviral drugs in many resource-limited settings. It is important to identify risk factors for second-line regimen failure.
Methods: HIV-infected children initiating protease inhibitor (PI)–containing second-line ART within the PHPT observational cohort study in Thailand between 2002 and 2010 were included. Treatment failure was defined as confirmed HIV type 1 RNA load >400 copies/mL after at least 6 months on second-line regimen or death. Adherence was assessed by drug plasma levels and patient self-report. Cox proportional hazards regression analyses were used to identify risk factors for failure.

Outcome: A total of 111 children started a PI-based second-line regimen. Median first-line ART duration was 1.9 years and median age at second-line initiation was 10.7 years. Fifty-four children (49%) experienced virologic failure, and 2 (2%) died. The risk of treatment failure 24 months after second-line initiation was 41%. In multivariate analyses, failure was independently associated with exposure to first-line ART for >2 years (adjusted hazard ratio [aHR], 1.8; P = .03), age >13 years (aHR, 2.9; P < .001), body mass index–for–age z score < –2 standard deviations at second-line initiation (aHR, 2.8; P = .03), and undetectable drug levels within 6 months following second-line initiation (aHR, 4.5; P < .001).

Conclusion: Children with longer exposure to first-line ART, entry to adolescence, underweight, and/or undetectable drug levels were at higher risk of failing second-line ART and thus should be closely monitored.

In summary, the high risk of failure observed within the first two years of PI-based second-line ART is explained by poor adherence to treatment and entry in adolescence. It is thus crucial to analyze and understand the causes of poor adherence.

Funding: Global Fund to Fight AIDS, Malaria and Tuberculosis; Oxfam GB THAA51; Ministry of Public Health, Thailand; Institut de Recherche pour le Développement (IRD), France.

Key publications.


This work was conducted by Rapeepan Suaysod, a Master degree student (Bioinformatics, Faculty of Science, Chiang Mai University) in the CMU-IRD research unit. She received advice from Asst. Prof. Dr. Patrinee Traisathit and Asst. Prof. Dr. Sukon Prasitwattanaseree (Faculty of Science, Chiang Mai University) and Dr. Gonzague Jourdain (PHPT). Rapeepan Suaysod received a student scholarship from the Graduate School and research assistantship scholarships from the Center of Excellence for Innovation in Analytical Science and Technology (I-ANALYST) and Mid-Career Researcher Program, Chiang Mai University, Thailand.

Active TB in HIV-infected children

Thailand is one of the 22 high tuberculosis (TB) burden countries listed by the WHO. We estimated the incidence of newly diagnosed active TB in HIV-infected children and compared survival rates of children with and without newly diagnosed active TB in a large HIV cohort in Thailand.

Status: started in 2014, ongoing.

Outcome: Of 589 ART-naïve children <15 years old enrolled in the PHPT cohort between 1999 and 2012 and with no history of TB, 320 (54%) were female. At ART initiation, median age was 6.2 years (IQR, 1.8-9.6), BMI-for-age z-score -0.8 standard deviations (-2.0 to 0.0), HIV RNA load 5.2 log10 copies/mL (4.7-5.7) and CD4 9% (2-17). Median follow-up was 7.6 years (3.2-9.7). Incidence rate of newly diagnosed active TB was 8/1,000 PYFU (95% CI, 6-12) (33 cases) and decreased with ART duration. Of the 33 cases, 9 died. Cumulative survival rates at 10 years were 67% (95% CI, 45%-82%) in children with newly diagnosed active TB and 91% (88%-93%) without (p<0.001).

In summary, a low incidence of newly diagnosed active TB was observed but HIV-infected children with active TB were at high risk of death. This may reflect the lack of adequate tools to screen and diagnose children for TB.

Funding: Global Fund to Fight AIDS, Malaria and Tuberculosis and Institut de Recherche pour le Développement (IRD), France.

Publication

3.3.2 HPV and cervical cancer

PapilloV study: HPV infections and cervical lesions in HIV-infected women in Thailand. A prospective study

Justification

Cervical cancer is caused by infection with High-Risk Human Papillomaviruses (HR-HPV). In Thailand, this cancer represents the second cause of death related to cancer in women. HIV infected women appear to be at high risk of cervical cancer in relation to a higher prevalence and longer persistence of HR-HPV infection. However, scarce data are available on the prevalence and incidence of cervical lesions in this population and on the distribution of the type of HR-HPV. The detection of HR-HPV in the cervix has been proposed as an alternative to pap-smear screening: its sensitivity is higher than Pap-smear’s and a self-sampling approach could increase its acceptability.

The objectives of the study were to 1) Assess the prevalence, incidence, persistence and clearance rates of cyto-histological anomalies of the cervix; 2) Evaluate the prevalence, incidence, persistence and clearance rates of HPV cervical infections; 3) Describe the HPV ecology: genotypes involved, types of infection (single or multiple); 4) Provide data to support the appropriate screening algorithm for these women combining Pap-smear and HPV testing.

Methods

The study is a multicenter prospective study, nested within the PHPT-Global Fund cohort study. All

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HIV-infected women (≥18 years, not virgin) enrolled in the PHPT cohort are proposed to participate. The follow-up of women consists of an annual gynecological exam with Pap-smear and HPV testing systematically performed. Women with abnormal Pap-smear or HR-HPV infection of the cervix are referred to undergo a colposcopy and in case of lesion, a biopsy and appropriate treatment if needed. The follow-up is planned for 3 years.

**Status and main results**

The enrollment was completed in June 2013: **829 women have been enrolled** and followed in the 24 hospital sites. At baseline, the prevalence of abnormal pap-smears is 9.5% and the prevalence of HR-HPV is 22.0%. These rates are much higher than what is reported in the general population. The follow-up of women is currently ongoing.

**Collaborators**

- Le Coeur S, Institut National d’Etudes Démographiques (INED, France); Jourdain G, Ngo-Giang-Huong N (IRD PHPT); Heard I, Centre National de reference HPV, Institut Pasteur, Paris, France; Aram Limtrakul, Nakornring Hospital; Nantasak Chotivanich, Chonburi Hospital; Chaiwat Putiyanun, Chiang Kham Hospital (Ministry of Public Health, Thailand). Samreung Rangdaeng, Faculty of Medicine, Chiang Mai University.

**Funding**: Institut National du Cancer (France), Fondation de France (France), Institut de Recherche pour le Développement (IRD), France.

**Publications**


**3.3.3 Long term consequences of HIV**

➤ Pilot study to assess the endothelial function in HIV infected patients on antiretroviral treatment through measurement of flow-mediated dilatation and its relationship with systemic immune activation, inflammatory and coagulation markers

**Background**: Long term follow-up of patients on antiretroviral therapy has revealed that HIV infected patients remain at increased risk of morbidity and mortality due to cardiovascular, metabolic, kidney or liver diseases. Impaired endothelial function is considered as a key event in the development of atherosclerosis and cardiovascular diseases.
**Objectives:** To evaluate the endothelial function in HIV infected patients who have received antiretroviral therapy for at least 3 years within the PHPT cohort and analyze its relation with different markers of immune activation, inflammation and coagulation.

**Methods:** This pilot study was conducted within the GFATM AIDS SSF (PHPT cohort) and enrolled a total of 70 patients between May 2012 and November 2012.

Endothelial function was assessed using a noninvasive test called flow-mediated dilatation (FMD), which measures the dilatation of an artery following a blood flow increase.

Several markers of immune activation (CD8+ CD38+ T-lymphocytes, soluble tumor necrosis factor alpha type two receptor –TNFrII), inflammation (high-sensitivity C-reactive protein or hsCRP, interleukin 6, soluble CD14, soluble vascular adhesion molecule-1 or sVCAM-1) and coagulation (D-Dimers) were measured in blood. Categorical variables were expressed as frequencies and percentages, and continuous variables as medians and interquartile ranges (IQR). Fisher’s exact test and Wilcoxon–Mann–Whitney test were used to compare categorical and continuous variables between groups.

**Outcomes:** A preliminary analysis showed that endothelial dysfunction was common in this group although all patients achieved viral suppression and were relatively young. Higher sVCAM-1 concentration was associated with higher risk of low flow-mediated dilatation (FMD). Preliminary results were presented as E-poster at the 11th International Congress on AIDS in Asia and the Pacific (ICAAP11) on 18-22 November 2013. Analyses of the relationship between endothelial dysfunction and immune activation markers are ongoing.

**Funding:** IRD, Global Fund.

**Publication**


### 3.3.4 Long-term evolution of lipids in HIV-infected adults and children

**Association between hyperlipidemia and high plasma efavirenz levels in children in the PHPT observational cohort, Thailand**

Antiretroviral therapy (ART) has been associated with metabolic abnormalities including lipid abnormalities. The long term consequences of such abnormalities in children are not well known but may be detrimental.

**Status:** started in 2011, completed.

**Outcome:** 82 children (46% male) initiated efavirenz+lamivudine+zidovudine or stavudine as first line regimen and had lipid and plasma efavirenz levels measured. 73% of children with higher efavirenz concentration had a viral load <400 copies/mL, versus only 44% with lower efavirenz concentration (p=0.01). In the multivariate analysis, factors associated with high cholesterol were high efavirenz concentration (p=0.03) and abnormal ALT levels at baseline (≥1.25 x ULN) (p=0.03), while high triglycerides were associated with older age (p=0.01) and HIV RNA above median at baseline (p=0.03).

**In summary,** children with high efavirenz concentrations were more likely to have high cholesterol but more likely to suppress viral replication. Before any dose reduction, the risk of viral breakthrough should be carefully considered.
Impact of antiretroviral treatment (ART) on the height

The objective is to describe the pattern of height evolution, also to create a mathematical function that can be used from birth to adulthood and to identify predictors of catch-up growth of HIV-infected naïve children. We modeled 18,596 body heights from 477 HIV-infected naïve children initiated therapy between 1999 and 2013, in Thailand. A mathematical function that can describe the pattern of height with age using nonlinear mixed effect model was built to identify predictors of catch-up height. Gender, type of ART, CD4 cell counts and HIV viral load at baseline were also examined for their effect on height following ART.

Outcome: The median age at ART initiation was 6.2 years (interquartile range (IQR) 1.8-9.6). The median duration of ART was 6.3 years (IQR 3.0-8.3). An empirical mixed effects model was developed to describe the age-related change of height. The overall height prediction was obtained from the sum of four components, defined by three phases described by their exponential functions with a lag time. ART significantly increases the height-growth-velocity, reducing the time to reach 50% of the height-growth in each phase.

In summary, these findings suggest that ART accelerates height-growth and that early initiation of ART insures rapid catch-up of the height.

Consequences of HIV-HBV/HCV co-infection

Long-term hepatitis B virus (HBV) response to lamivudine-containing highly active antiretroviral therapy in HIV-HBV co-infected patients in Thailand (Research for Ph.D dissertation, Faculty of Associated Medical Sciences, Chiang Mai University)

In Thailand, approximately 8% of HIV-infected patients are co-infected with HBV. The majority of them initiate first-line highly active antiretroviral therapy containing lamivudine (3TC-containing-HAART) and long-term virological response of HBV to lamivudine-containing HAART in co-infected patients is not well known. We thus evaluated the long-term effect of 3TC on HBV replication in 30 HIV/HBV co-infected patients receiving 3TC-containing-HAART. HBV DNA, HIV RNA, absolute CD4 and CD8 T-cells counts, and liver enzymes were measured at baseline, 3 months, 12 months and then every 6 months up to 5 years.

Outcome: Prior to 3TC-based HAART, median HBV DNA level was 7.35 log_{10} IU/mL (IQR: 5.55-8.07). At 12 months, 23 (67%) patients achieved HBV DNA suppression (≤2.18 log_{10} IU/mL): 100% of HBeAg-negative patients and 47% of HBeAg-positive patients. Seventy-three percent of these patients had HIV RNA <50 copies/mL. The cumulative rates of maintained HBV-DNA suppression among the 23 patients who achieved HBV-DNA suppression were 91%, 87%, and 80% at 1, 2, and 4 years respectively. Of 17 patients who maintained HBV-DNA suppression while still on 3TC, 4 (24%) lost HBsAg and 7 of 8 (88%) HBeAg-positive patients lost HBeAg at their last visit (median duration, 59 months). HBV breakthrough was observed only in HBeAg-positive patients and 6 of 7 patients presenting HBV breakthrough had the rtM204I/V mutations associated with 3TC resistance along with rtL180M and/or rtV173L.

In summary, these results suggested that long-term suppression of HBV replication is an additional benefit provided by 3TC-containing HAART for a significant number of HIV/HBV co-infected patients and particularly those with HBeAg negative.
Collaborators

- Alain Goudeau, Université François-Rabelais de Tours, France
- Catherine Gaudy-Graffin, Université François-Rabelais de Tours, France
- Alain Moreau, Université François-Rabelais de Tours, France
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- Guttiga Halue, Phayao Hospital, Thai MoPH
- Yuwadee Buranawanitchakorn, Chiang Kham Hospital, Thai MoPH
- Sura Kunkongkapan, Mae Sai Hospital, Thai MoPH
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Funding: This work was supported by Agence Nationale de Recherches sur le Sida et les hépatites virales (grant number ANRS 12-179); the Global Fund to fight AIDS, TB and Malaria; the Institut de Recherche pour le Développement (IRD), France; and Thailand International Development Cooperation Agency (TICA), Thai Ministry of Foreign Affairs. Woottichai Khamduang (Ph.D. student, Faculty of Associated Medical Sciences, Chiang Mai University) received scholarships from the IRD, the Franco-Thai cooperation program in Higher Education and Research, the Faculty of Associated Medical Sciences, Chiang Mai University, and the French Ministry of Foreign Affairs.

Publications


⇒ Evolution of patients co-infected with HIV and HBV in an adult cohort in Thailand

It is generally considered that HBV infection does not affect the evolution of HIV infection. However, the co-infection with HIV increases the risk of liver cirrhosis and hepatocellular carcinoma. This project aims to better understand the evolution of patients co-infected with HIV and HBV, in particular estimate the rates and identify risk factors of mortality and virologic failure in HBV-HIV co-infected patients.

Status: started in 2014, ongoing.
Outcome

Study population includes 1,708 HIV-infected adults at ART initiation. Median age was 32.0 years (IQR: 27.5 - 37.6), and 77.7% were female. HBV infection status was not associated with mortality, both in the Cox univariate analysis (p=0.337) and multivariate analysis (p=0.953) after adjustment on confounders significant in the univariate analyses (including gender, BMI and CDC stage). Among older patients and patients newly enrolled in the cohort, however, mortality risk was significantly higher in HBV-HIV co-infected patients than in HIV mono-infected patients in univariate analysis.

In summary, although overall HBV infection status was not independently associated with mortality, HBV infection increased the risk of death in male and older patients.

Funding: Global Fund to Fight AIDS, Malaria and Tuberculosis and Institut de Recherche pour le Développement (IRD), France.

Evolution of adult patients co-infected with HIV and HCV

This project, which has just started, aims to estimate the prevalence of HCV infection in a cohort of treated HIV infected patients, to describe HIV-HCV co-infected patients in terms of demographic characteristics, mortality, complications of chronic hepatitis and virologic failure, and to estimate the survival rate without hepatic complication.

Status: started in 2014, ongoing.

Outcome (preliminary results): Overall, 5.4% of all HIV-infected adults enrolled in the PHPT adult cohort had positive anti HCV antibodies. On the 98 patients who had a HCV RNA test, 59 (60%) had at least one HCV RNA detectable. Almost half of the patients are deceased (7%), lost to follow up (23%) or have withdrawn from the study (16%), but 28 co-infected patients are still on follow up.

Funding: Global Fund to Fight AIDS, Malaria and Tuberculosis and Institut de Recherche pour le Développement (IRD), France.

3.4 Towards individualized treatments

Renal safety of tenofovir in HIV-1 infected adults in Thailand

Background

Access to tenofovir (TDF) as part of first line therapy in developing countries is expanding but it is not recommended in Thailand to use this drug as part of a first line regimen due to uncertainties regarding its renal toxicity.

Methods
Data from HIV-infected adult patients initiating HAART containing either tenofovir or zidovudine between May 2005 and April 2007 in the PHPT-3 clinical trial [ClinicalTrials.gov: NCT00433030] were analyzed. Changes in creatinine clearance (CrCl) were compared in 454 patients initiating tenofovir versus 175 initiating zidovudine. Sixty-two percent were female, median age 35 years, CrCl 99 mL/min/1.73m2.

**Outcome**

Patients initiating tenofovir had lower baseline median weight (52 kg) compared to zidovudine (56 kg, p=0.01). Median follow-up was 5.4 years for TDF and 6.2 years (5.9-6.4) for zidovudine. Over the first 5 years, 14 tenofovir (3%) and 11 zidovudine (6%) patients died. 38 tenoforv (8%) and 11 zidovudine (6%) were lost/withdraw. Risk of a >25% CrCl reduction was 43% with tenofovir and 36% with zidovudine (Hazard Ratio [HR] 1.21 95%CI p=0.19). After adjustment for baseline weight, CrCl, age, and blood pressure, the HR was 1.39 (1.03-1.87, p=0.03) suggesting a higher risk of >25% CrCl decline in the tenofovir group.

**No Relationship Between Drug Transporter Genetic Variants and Tenofovir Plasma Concentrations or Changes in Glomerular Filtration Rate in HIV-infected Adults**

**Background:** Tenofovir disoproxil fumarate (TDF) is recommended as part of combination antiretroviral therapy in treatment-naïve patients. Tenofovir is primarily excreted unchanged through the kidneys. Drug transporters play a key role in the movement of tenofovir through the kidney. Host genetics may contribute towards TDF-associated kidney disease susceptibility. We investigated the association between drug transporter genetic polymorphisms with tenofovir plasma concentrations, and changes in kidney function.

**Methods:** A retrospective analysis of antiretroviral naive HIV-infected adults in Thailand who initiated TDF as part of an NNRTI-based regimen within the PHPT cohort [ClinicalTrials.gov: NCT00433030]. Ten single nucleotide polymorphisms (SNPs) were assessed: ABCC2 (rs717620, rs2273697, rs8187694, rs3740066, rs8187710), ABCC4 (rs1751034), ABCC10 (rs9349256, rs2125739) and SLC22A2 (rs3127573, rs316009). Differences in tenofovir trough concentrations (C24) and change in creatinine clearance (CrCL) between genotypes after 1 and 3 years of TDF treatment were assessed.

**Outcome:** 238 adults (58% female) were included. At baseline, median (interquartile range) age was 36 years (31-42), weight 52 kg (48-59) and CrCL 89 mL/min (74-105). For each SNP, no significant difference in C24 was observed between genotypes. A weak trend towards a lower C24 with ABCC2 -24 CT/TT variants at 1 year (p=0.06) and higher C24 with ABCC4 3463 AG/GG variants at 1 year (p=0.07) were observed but q-values were less significant (q=0.25). None of the SNPs were significantly associated with changes in CrCL over 3 years of TDF treatment.

Overall, drug transporter polymorphisms implicated in tenofovir excretion and/or associated nephrotoxicity were not associated with tenofovir C24 or changes in CrCL after 3 years of TDF treatment within a 1st-line NNRTI-based regimen.

**Funding Support:** The National Research University Project under Thailand's Office of the Higher Education Commission, The Global Fund to fight AIDS, Tuberculosis, and Malaria Thailand (Grant Round 1 sub recipient PR-A-N-008); National Institutes of Health, NICHD (HD042964), USA, Ministry of Public Health, Thailand and Institut de Recherche pour le Developpement, France.

**Key publications**

3.5 Understanding the relationships between host, pathogens, and drugs to design interventions

3.5.1 Metabolic anomalies

Incidence and risk factors of diabetes in HIV-infected adults on ART in Thailand

Use of several antiretrovirals (ARVs) has been shown associated with a higher risk of diabetes in HIV-infected adults. We estimated the incidence of new-onset diabetes and assessed the association between individual ARVs and ARV combinations (ARVcs), and diabetes in a large cohort in Thailand.

Status: started in 2013, completed.

Outcome

Study population consists of 1,594 HIV-infected ART-naïve adults without diabetes before ART initiation; 1,217 (76%) were female. Median age at antiretroviral therapy (ART) initiation was 32.5 years. The incidence rate of diabetes was 5.0 per 1,000 PYFU (95% confidence interval, 3.8-6.6) (53 cases). In analyses adjusted for potential confounders, exposure to stavudine+didanosine (adjusted Hazard Ratio [aHR]=3.9, p=0.001) and cumulative exposure ≥1 year to zidovudine (aHR=2.3 versus no exposure, p=0.009) were associated with a higher risk of diabetes. Conversely, cumulative exposure ≥1 year to tenofovir (aHR=0.4 versus no exposure, p=0.02) and emtricitabine (aHR=0.4 versus no exposure, p=0.03) were associated with a lower risk.

In summary, the incidence of diabetes in this predominantly female, young, lean population was relatively low. While stavudine and didanosine have now been phased out in most ART programs, our analysis suggests a higher risk of diabetes with zidovudine, frequently prescribed today in resource-limited settings.

Funding: Global Fund to Fight AIDS, Malaria and Tuberculosis and Institut de Recherche pour le Développement (IRD), France.

Key publications


3.5.2 Immunological, virological and host determinants of perinatal transmission of infectious diseases

Dynamics of variants during HCV transmission and role of neutralizing antibodies: analysis in the context of mother to child transmission

This is a collaborative project with Tours University, France and the Faculty of Associated Medical Science, Chiang Mai University.

Status: This project has been recently approved for funding and will start this summer. A PhD student in France and a Master degree student from Thailand will be involved in the conduct of this project.

Background: Mother-to-child transmission (MTCT) of HCV is estimated to occur in about 5% of infants born to HCV-infected mothers. Major risk factors are high maternal HCV RNA level and maternal HIV-coinfection. Homogeneous HCV variants are generally transmitted to the infant despite
the presence of a heterogeneous viral population in the mother. Few studies have analyzed the selective process occurring during MTCT.

**Objectives:** To identify the viral molecular determinants associated with a stronger capacity of maternal HCV strains to be transmitted to the infant.

**Methods:** For this study, we will assess HCV status in the mothers by testing HCV RNA in all women found positive for anti-HCV antibody. Secondarily, all infants born to HCV viremic mothers will be tested for HCV RNA at birth, 6 to 8 weeks and four months of age.

We will analyze the viral diversity in mother-infant pairs using the Single Genomic Amplification (SGA) technology (allow the detection at very low level of minor variants) targeting E1/E2 genes encoding for the most variable proteins. E1/E2 sequence patterns and viral evolution will be analyzed between mother and infants variants. Sites undergoing selective pressure will be predicted among the various epitopes described across E1 and E2 glycoproteins. Retroviral pseudotypes bearing HCV envelopes identified in HCV infected mothers and their infected infants will be produced and evaluated for their sensitivity to neutralization by maternal and heterologous plasma. Ethical approval to analyze these patients’ stored samples will be sought from the Ethics Committee of the Faculty of Associated Medical Sciences, Chiang Mai University.

**Funding:** *Initiative Académique 2014, région Centre and French Ministry of Higher Education and Research.*

**Properties of HIV-1 envelope glycoprotein in perinatally infected children**

This is a collaborative project with Tours University, France and the Faculty of Associated Medical Science, Chiang Mai University.

**Background:** Despite a heterogeneous viral population in HIV-infected mothers, homogeneous viral variants are generally transmitted to the infant, suggesting that a limited number of maternal viral variants are selected and establish infection in the infant. Maternal neutralizing antibodies (Nabs) are among the selective factors that may be responsible for this genetic bottleneck.

**Objectives:** To identify molecular determinants of viral evolution perinatal HIV transmission.

**Methods:** We assessed the antigenic and functional properties of pseudotyped viruses expressing gp120 encoded by env clones issued from mother-infant pairs infected by CRF01_AE viruses. We compared the sensitivity of those pseudotyped viruses to entry inhibitors and to neutralization by maternal plasma collected during pregnancy (before initiation of zidovudine (ZDV) prophylaxis) and by broadly neutralizing human monoclonal antibodies (mAbs) (b12 directed against an epitope overlapping the CD4-binding site (CD4BS) and PG9 and PG16 that recognize a quaternary neutralizing epitope formed from conserved regions of V1/V2 and V3 variable loops). We also compared infectivity levels and Env processing and incorporation levels of maternal and infant pseudotyped virus. We analyzed the sequences to identify potential positions conferring resistance to mAbs and confirmed the impact of the identified positions by site-directed mutagenesis.

**Outcomes:** We found that transmitted viruses present in infants and variants present in their infected mothers display a wide, but indistinguishable, spectrum of biological properties. However, all transmitted viruses in infants were more sensitive to neutralization by PG9 and PG16 than the maternal variants. Two gp120 cross-clade conserved residues, a lysine at position 168 in the V2 loop and an isoleucine at position 215 in the C2 region, were associated with resistance to PG9 and PG16. We confirmed both in clades B and CRF01_AE that the substitutions K168E and I215M have a major impact on PG9 and PG16 neutralization sensitivity of pseudotyped viruses.

**Publications:**

type 1 variants of different clades are involved in PG9 and PG16 resistance to neutralization. J Gen Virol 93:1495-505.

**Analysis of Factors Contributing to Immune Reconstitution in HIV-Infected Patients during Combination Antiretroviral Therapy**

**Background:** Antiretroviral therapy results in viral suppression and immune reconstitution in most patients with advanced HIV disease. However, some individuals present discordant virological and immunological responses. IL-7 may play a major role in regulating T-cell development and homeostasis during HAART. Elevated IL-7 levels are thought to be due to increased production by homeostatic feedback, decreased receptor-mediated clearance, or both.

**Objectives:** To determine factors contributing to partial response (PR) to cART.

- To measure levels of IL-7α, sIL-7Ra and IL-7Rα and TREC.
- To analyze their relationships with immune reconstitution among those with full response and those with partial response to cART.

**Methods:** HIV-infected patients followed within the PHPT-GFATM cohort study and have received at least 5 years cART were included in the analysis. Full response (FR) was defined as CD4 cell count ≥500 cells/µL and HIV RNA load undetectable and partial immune response (PR) as CD4 cell count < 500 cells/µL and HIV RNA load undetectable. Plasma and peripheral blood mononuclear cells were collected for the measurement of IL-7, soluble IL-7Rα (sIL-7Rα or sCD127), using ELISA techniques. Thymic output or T cell receptor excision circles (TRECs) were measured using real-time quantitative PCR. Additionally, levels of CD127 expression on PBMCs, lymphocytes, T-helper and cytotoxic T cells isolated from EDTA blood were analyzed by flow cytometry. Analysis is ongoing.

**Outcomes:** Preliminary results show that older age and percentage of PBMC expressing CD127 were associated with partial response to ART. Levels of IL-7, sIL-7Ra and TRECs were not statistically significant different between patients with full response (FR) and those with partial response (PR) to cART.

### 3.5.3 Hematological safety of antiretroviral drugs and thalassemia

**Background:** It is unclear whether ARV used for the prevention of HIV mother-to-child transmission affects the hematological evolution in fetuses who are thalassemia carriers, and if it causes severe anemia which complicates the laboratory diagnosis of thalassemia.

**Objective:** To investigate the effects of antiretroviral (ARV) drugs on hematological parameters and thymic function in HIV-uninfected newborns of HIV-infected mothers.

**Methods:** Cord blood samples of newborns from 49 HIV-uninfected and 26 HIV-infected mothers were tested for hematological parameters using automatic blood cell count. T-cell receptor excision circles (TRECs) levels in cord blood mononuclear cells (CBMCs), CD4+ and CD8+ T-cells were quantified using real-time PCR.

**Outcomes:** Newborn of HIV-infected mothers tended to have lower mean hemoglobin levels, red blood cell (RBC) counts, and hematocrit as well as lower median TRECs in CD4+ T-cells than newborns of HIV-uninfected mothers. ARV drugs may modify hematological parameters and thymic function in HIV-uninfected newborns of HIV-infected mothers.

**Publication**


### 3.5.4 Resistance pathways

**Background:** Knowledge of resistance pathways is crucial for optimizing the sequence of antiretroviral drugs to be given to HIV-infected patients. The World Health Organization Antiretroviral Treatment Guidelines has recommended phasing-out stavudine because of its risk of long-term toxicity.
**Objectives:** To identify the cross-resistance patterns associated with first-line stavudine failure to help select the best ARV options for second-line therapy in settings where resistance testing is rarely available.

**Methods:** In addition to the analysis conducted with the resistance data obtained within the PHPT-GFATM cohort study, we have participated in the analysis of patterns of resistance mutations in patients failing their first line-ARV in Cambodia and contributed to an international analysis to identify the best ARV options in countries phasing out stavudine.

**Outcomes:** Results of the analyses have shown that specific mutations can emerge with particular HIV subtype under stavudine; for example K65R was more often seen with subtype C and CRF01_AE, the most prevalent subtype circulating in Southeast Asia. These results will contribute to assist country ARV programs in selecting the best ARV options second-line therapy in a context of limited resources and phase out of stavudine.

**Publications**


**3.5.5 Prediction of HIV-1 co-receptor usage in Thai population**

**Background:** HIV-1 enters target cells through the sequential binding of the envelope glycoprotein (gp120) to CD4 and a chemokine receptor, mainly CCR5 and CXCR4. Prior to using ARV drugs such as inhibitors of HIV entry, it is necessary to identify which co-receptor is used by the patient virus population.

The 2 bioinformatics tools currently available (Geno2pheno developed by Max-Planck-Institut Informatik and WebPSSM by Mullins laboratory at University of Washington) to infer the coreceptor usage from the amino acid sequence of V3 of the patient virus were built using data for subtype B viruses, most prevalent in North America and Europe. In Thailand and South-east Asia, the most prevalent strain is CRF01_AE.

**Objective:** To develop specific bioinformatics tools to evaluate for CRF01_AE virus the correlation between genotype-phenotype for CRF01_AE virus and to predict the co-receptor tropism.

- To develop bioinformatics tools (computational approaches) to predict the co-receptor usage by CRF01_AE subtype using data from V3 sequence and evaluate its prediction power
- To compare co-receptor usage determined by patient virus culture (phenotypic tropism assay) with the V3 amino acid sequences.

**Methods:** The support vector machine (SVM) method was used to classify HIV-1 coreceptor usage. The logistic model tree (LMT) was used to select relevant features and identify and remove irrelevant and redundant information to improve the predictive performance. A total of 273 sequences of the V3 region of HIV-1 gp120 from individual patients were retrieved from the Los Alamos HIV database; 177 were of R5 isolates and 96 of X4 phenotype: (http://www.hiv.lanl.gov/components/sequence/HIV/search/search.html). These sequences were used to identify co-receptor usage and evaluate the concordance between the newly developed tool and available bioinformatics tools.
Outcomes: The SVM based LMT method provided a predictive performance which is similar to the maximum performance in all other models. Using a ten-fold cross-validation of 273 sequences, the new tool achieved 97.8% accuracy, 97.7% specificity, and 97.9% sensitivity. Further studies are ongoing to validate this tool on data from clinical isolates from HIV-1 infected patients in Thailand and to confirm whether these positions may influence functional properties of coreceptor usage.

Publication


3.6 Towards sustainability and effective coverage

3.6.1 LIWA (Living With Antiretrovirals): Socio-demographic and economic evaluation of a community based antiretroviral program in Northern Thailand

Justification

While antiretroviral treatments dramatically reduce the morbidity and mortality associated with HIV/AIDS and transform HIV infection into a chronic disease, there are several constraints for patients (burden related to medications and their side effects), and for the society (cost and organization of care).

Methods: A life-event history survey of patients with HIV treated with antiretrovirals in 4 hospitals in northern Thailand and from a random sample of the general population of the same sex, age and place of residence of the patients (N = 1013) was initiated in 2007. The questionnaire explores family history, residential, educational, financial, but also the history of HIV infection, experiences of discrimination, and finally the sexual and reproductive lives.

Status: The study started in 2007 and is now completed.

Main results

Women had more access to HIV testing and treatment and analyzed its causes, distinguishing the demographic and socio - behavioral factors [Le Coeur et al., 2009].

Antiretroviral treatment was associated with a better intergenerational relationships [Lelièvre, et al. 2011].

Patients’ sexual life appeared similar in treated patients and controls [Le Coeur et al. 2014].

Collaborators

- Eva Lelièvre, Institut National d’Etudes Démographiques (INED, France);
3.6.2 TEEWA (TEEns living With Antiretrovirals): the impact of antiretrovirals on the lives of adolescents born with HIV in Thailand

A socio-demographic & economic evaluation of a community based ARV program in Northern Thailand.

Justification

Children born with HIV who receive antiretroviral (ARV) therapy have increasingly high survival rates and are now entering adolescence and adulthood. However, reports suggest higher treatment failure and mortality rates in adolescents. In resource-limited settings, large numbers of children born with HIV who received antiretrovirals (ARV) are now reaching adolescence. The 'Teenagers Living with Antiretrovirals' (TEEEWA) study investigates the living circumstances of these adolescents as well as their HIV history.

Methods

The data collection consists of paired interviews: a self-administered questionnaire filled by the HIV-infected adolescent receiving ARV linked to the interview of his/her caregiver who provides the difficult or sensitive information about the adolescents' life. Children living in family setting as well as children living in orphanages participate in the study. A reference group is composed of uninfected adolescents matched by age, sex and area of residence drawn from the general population or of uninfected adolescents living in orphanages.

Status

Between 2012 and 2014, 941 HIV-infected adolescents aged 12 to 19 years were surveyed in 20 hospitals and 7 orphanages throughout Thailand as well as 694 uninfected youth in the general population or in orphanages.

Main results

We were able to document the living circumstances of the adolescents born with HIV in Thailand. Among those living in family environment, 85% have lost one or both parents. One third is cared of by their grandparents and one quarter by their uncles or aunts.

Most adolescents were aware of their HIV status, but still 10% did not know that they were infected with HIV, and for 3% of them, the caregivers did not know whether they were informed.

A high proportion (24%) of caregivers reported that their child had experienced discrimination, in particular in the school setting.

Our study also demonstrates that the absence of close relatives to look after them, global poverty, physiological changes related to puberty increase the risk of treatment failure. In contrast, orphanage environment appears protective.

Collaborators

- Eva Lelièvre, Institut National d’Etudes Démographiques (INED, France);
- Surush Suwunta, Parinya Jongpajitsakol, (PHPT/IRD);
- Intira Collins, MRC, London, UK

Funding: ANRS 12141 (National Agency for Research on AIDS and Viral Hepatitis, France)

Key publications


Figure: Publication of TEEWA study in the cover page of ‘IRD scientific news’.

3.6.3 Economic evaluation of HIV prevention, diagnosis and care interventions in adults and children in the Thai setting

Several cost-effectiveness studies were performed:

⇒ Cost-effectiveness of early infant HIV diagnosis and immediate antiretroviral therapy in Thailand

Justification: It has been shown that the risk of mortality among HIV infected children is the highest during the first year of life, with up to 40% mortality at one-year if untreated in resource limited setting. Provision of antiretroviral therapy (ART) has dramatically reduced HIV related morbidity and mortality in children. The objective of this analysis was to assess the cost-effectiveness of early infant HIV diagnosis (EID) using DNA PCR of HIV-exposed non-breastfed infants and immediate initiation of antiretroviral therapy (ART) in HIV-infected children under 24-months in Thailand, as per World Health Organization (WHO) guidelines.

Methods: A decision analytic model of HIV diagnosis and disease progression in HIV-infected children compared 3 cases scenarios: 1) EID with immediate ART (Early-Early); 2) EID with deferred ART based on immune/clinical criteria (Early-Late); 3) deferred diagnosis by clinical and serology and deferred ART (Reference arm).

The model was populated with data on survival and costs of EID and ART from the Thai PHPT pediatric cohort and the literature. Incremental cost-effectiveness ratio in US dollars per life-year saved (LYS) was compared against the Reference arm.
Main result: Early HIV diagnosis and immediate ART was highly cost-effective in Thailand. With improved coverage and efficacy of prevention of mother-to-child transmission of HIV this strategy becomes even more affordable with less HIV-infected children requiring lifelong treatment. Our findings strongly support the adoption of WHO recommendations as part of routine care.

Publication


Hospitalization trends, costs, and risk factors in HIV-infected children on antiretroviral therapy

Justification: There were scarce data on hospitalization trends in children receiving antiretroviral therapy (ART), an important indicator of morbidity and health service utilization. The objectives were to describe the rates of hospitalization, the primary causes, outcomes and cost of inpatient care over time on ART and to assess risk factors associated with hospitalization and frequency of admission.

Methods: Using data from the PHPT pediatric cohort in Thailand, hospitalization rates per 100 person-years (PY) were calculated from ART initiation to death or last follow-up. Costs to the health care provider were calculated using inpatient unit estimates for Thailand multiplied by duration of admission. Zero inflated Poisson models were used to examine factors associated with early (<12-months of ART) and late hospitalization (≥12-months of ART) and frequency of admissions.

Main results: 578 children initiated ART, median follow-up was 64 months (IQR 43-82); 211 (37%) children were hospitalized with 451 admissions. Hospitalization rates declined from 63 per 100PY <6-months to ~10 per 100PY after 2 years of ART, while hospitalization cost decreased from $35 per patient-month to under $5, respectively.

Hospitalization rates and costs peaked in the first year of ART and rapidly declined thereafter. Factors associated with hospitalization include baseline age, wasting/stunting and advanced disease stage. Earlier treatment initiation before advanced disease progression may reduce hospitalization and alleviate demands on healthcare systems.

Funding: The Global Fund to fight AIDS, Tuberculosis and Malaria; Institut de Recherche pour le Développement (IRD), France; International Maternal Pediatric Adolescents Aids Clinical Trials Group (IMPAACT); The National Institutes of Health, US; Ministry of Public Health, Thailand; Oxfam Great Britain, Thailand; United Kingdom Medical Research Council Doctoral Training account Studentship.

Key publications

3.6.4 Access to, delivery of and effective use of health services among minority groups and international migrants in Thailand

Access to Care in Communities (ATC)

Beginning in 2010, ATC has collected data to compare population characteristics, knowledge of HIV transmission, prevention, diagnosis and treatment, use of HIV-related health services, stigma (intent to avoid or prevent contact with HIV infected individuals), constraints to use of health services in women who have delivered one or more children, and the women’s partners in rural majority ethnic Northern Thai, and ethnic minority Chinese, Hmong and Lahu communities near the Thai-Myanmar border.

Outcomes

As of 01 December 2015 a total of 743 women and 584 men have been interviewed with data coded and entered into computer (Table 1). Additional interviews are being conducted in Chinese, Lahu and Tai Yai communities (data not yet processed)

Table 1. Composition of Access to care Project Survey Population

<table>
<thead>
<tr>
<th>Survey Respondents</th>
<th>Predominant Ethnicity of Surveyed Communities</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chinese</td>
<td>Hmong</td>
</tr>
<tr>
<td>Women</td>
<td>247</td>
<td>179</td>
</tr>
<tr>
<td>Men</td>
<td>187</td>
<td>150</td>
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<tr>
<td>Total</td>
<td>434</td>
<td>329</td>
</tr>
<tr>
<td>Surveyed communities</td>
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<td>2</td>
</tr>
</tbody>
</table>

We have compared socio-economic characteristics, knowledge and behavior of women from Northern Thai communities (our "comparison standard") vs. women from ethnic minority communities, and have compared within ethnic minority communities between women who are non-citizen migrants vs. Thai citizens, or those who speak and understand Thai language vs. those who cannot, or who have health insurance vs. those who do not.
Women from ethnic minority communities, as compared with women from Northern Thai communities are significantly likely to: have less economic, material and social resources, be poorly-informed about HIV transmission, prevention, diagnosis and treatment, be more likely to stigmatize people living with HIV, to be are less likely to use modern health services and more likely to experience constraints to using the services, whether or not the women from the minority communities have government-supported health insurance.

Within ethnic minority communities, women who do not have government-supported health insurance compared with women from the same communities who are insured are also likely to: have less economic, material and social resources, be poorly-informed about HIV transmission, prevention, diagnosis and treatment, be more likely to stigmatize people living with HIV, to be are less likely to use modern health services and more likely to experience constraints to using the services. For the most part, significant differences remain between insured members of the ethnic minority communities.

Among the ethnic minorities, Chinese and Lahu women are more likely than Hmong women to have significantly fewer resources than Northern Thai women, significantly less knowledge, and make significantly less use of health services; however, Chinese women and Hmong women (who are more often similar to Northern Thai women in terms of resources and knowledge of HIV), remain significantly more likely to intend to avoid (stigmatize) people living with HIV, and less likely to use health services.

Collaborators. Personnel from district and sub-district hospitals and health centers in Chiang Dao District, Chiang Mai Province, Village Health Volunteers from communities in the study population, Chiang Dao Community Advisory Board.

Funding: Research funded by Oxfam UK, Global Fund to fight AIDS, Tuberculosis and Malaria, Thailand - United States Educational Foundation (TUSEF/Fulbright Thailand), and Generosity in Action.

Key publications


4. COMPLETE LIST OF PUBLICATIONS

From July 2011 to December 2015, lecturers and researchers of Chiang Mai University in collaboration with the network researchers from several institutions worldwide published 43 articles in International journals, 20 oral presentations at National/International Conferences and 37 posters presentations as follows:

4.1 Published Articles

43 articles were published in International journals under the collaboration between Chiang Mai University and the research network group from several institutions worldwide. 19 articles included authors affiliated with Chiang Mai University.

July 2011 to December 2011


Published Articles – 2012


Published Articles – 2013


Published Articles – 2014


Published Articles – 2015


4.2 Oral presentations at National/International Conferences

Total 20 oral presentations are as follows:

**Oral presentations - July 2011 to December 2011**


**Oral presentations – 2012**


Oral presentations – 2013


Oral presentations – 2014

PENTA-18 Team. Final results of KONCERT: a randomized non-inferiority trial of QD vs BD LPV/r dosing in children. 21st Conference on Retroviruses and Opportunistic Infections, Boston, USA. 3-6 March 2014, Abstract #LB74; Oral Presentation


Oral presentations – 2015


4.3 Poster presentations at National and International Conferences

Total 37 posters presentations are as follows:

Posters - July 2011 to December 2011


Posters – 2012


• Cressey TR, Best BM, Achalapong J, Stek A, Suriyachai P, Wang J, Shapiro D, Watts DH, Smith E, Capparelli EV, Kreitchman R, Mirochnick M, for the IMPAACT P1026s Study Team Effect of Pregnancy on Pharmacokinetics of Indinavir boosted with Ritonavir. 13th International Workshop on Clinical Pharmacology of HIV Therapy, Barcelona, Spain, 16-18 April, 2012; Abstract P37, Poster


Posters – 2013


- Aupribul L, Narkbunnam T, Sirisanthana V, Wittawatmongkol O, Phongsamart W, Sudjaritruk T, Cressey TR, Chokephaibulkit K. 48-week Safety of Tenofovir When Administered According to Weight Band Dosing in HIV-infected Children >= 15 Kg as Part of a Once-daily HAART Regimen. CROI 2013, March 3-6, 2013 Georgia World Congress Center, Atlanta, USA, Poster#972


Posters – 2015


5. CONFERENCES & TRAININGS (July 2011 – October 2015)

5.1 International Symposia organized by the PHPT-AMS research unit


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### 5.2 External trainings involving the PHPT-AMS research unit as organizer or provider of trainer(s).

<p>| Title / Topic                                                                 | Start date  | End date  | Location                                                 | Organizer          | Participants |
|------------------------------------------------------------------------------|-------------|-----------|-------------|--------------------------------------------------------|-------------------|--------------|
| Bayesian statistics and <em>WinBUGS</em> seminar                                     | 2011-07-05 | 2011-07-05| Faculty of Science, Chiang Mai University               | PHPT               | 39           |
| Youths meeting at Saturday Clinic in Nakornping hospital                     | 2011-07-09 | 2011-07-09| HIV clinic, Nakornping hospital                         | PHPT, Nakornping hospital | 25           |
| IMPAACT P1083 Pharmacy training                                              | 2011-07-22 | 2011-07-22| The Empress Hotel, Chiang Mai                          | PHPT               | 23           |
| Training on &quot;How to assure Quality of Laboratory tests&quot; and &quot;Patient sample transportation&quot; | 2011-08-05 | 2011-08-05| Maninarakorn Hotel, Chiang Mai                         | PHPT Laboratory    | 69           |
| Management of Abacavir Hypersensitivity                                       | 2011-08-05 | 2011-08-05| PHPT office, Chiang Mai                               | PHPT               | 21           |
| Management of Abacavir hypersensitivity                                      | 2011-08-09 | 2011-08-09| PHPT office, Chiang Mai                               | PHPT               | 32           |
| Phayao kid camp                                                               | 2011-08-13 | 2011-08-14| Phayao college of agriculture and technology           | CAB Phayao         | 46           |
| Training evaluation data management system for ARV treatment program         | 2011-08-15 | 2011-08-19| Mahosot Hospital, Laos                                | ESTHER             | 16           |
| Advanced Statistical Methods for Healthcare Research                          | 2011-08-22 | 2011-08-23| Kantary Hills Hotel, Chiang Mai                        | PHPT               | 49           |
| PHPT-5 Phase 2 Implementation                                                 | 2011-08-22 | 2011-08-22| Richmond Hotel, Nonthaburi                            | PHPT               | 76           |
| PHPT-5 Phase 2 Implementation                                                 | 2011-08-23 | 2011-08-23| Hat Yai Hospital, Song Kla                            | PHPT               | 34           |
| Papillomavirus Study Implementation                                          | 2011-08-24 | 2011-08-24| Montien Hotel, Chonburi                               | PHPT               | 20           |</p>
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<td>HIV Counselling training</td>
<td>2014-06-24</td>
<td>The Empress hotel, Chiangmai</td>
<td>PHPT</td>
<td>199</td>
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<tr>
<td>Good Clinical Practice, Human Subject Protection, and Institutional review board (IRB)/ Independent Ethics Committee (IEC)</td>
<td>2014-07-22</td>
<td>Wiang Inn hotel, Chiangrai</td>
<td>PHPT</td>
<td>38</td>
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<tr>
<td>iTAP Counseling Training</td>
<td>2014-07-28</td>
<td>Richmond Hotel, Nonthaburi</td>
<td>PHPT</td>
<td>46</td>
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<tr>
<td>HCV Co-investigators meeting</td>
<td>2014-09-01</td>
<td>Amari airport hotel, Bangkok</td>
<td>PHPT, with Prof. Stanislas Pol</td>
<td>22</td>
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<tr>
<td>Training: Contents &amp; development of manuals for HCV treatment</td>
<td>2014-10-30</td>
<td>Imperial Maeping hotel, Chiang Mai</td>
<td>PHPT</td>
<td>24</td>
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<tr>
<td>iTAP Co-investigators meeting</td>
<td>2015-03-23</td>
<td>Amari Airport hotel, Bangkok</td>
<td>PHPT</td>
<td>64</td>
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<tr>
<td>iTAP Study drug dispensation training</td>
<td>2015-03-11</td>
<td>at 17 iTAP study sites (hospitals)</td>
<td>PHPT</td>
<td>53</td>
<td></td>
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<tr>
<td>iTAP Co-investigators meeting</td>
<td>2015-06-25</td>
<td>Amari airport hotel</td>
<td>PHPT</td>
<td>53</td>
<td></td>
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<tr>
<td>iTAP Co-investigators meeting, following iTAP DSMB meeting</td>
<td>2015-08-17</td>
<td>Amari Don Muang hotel, Bangkok</td>
<td>PHPT</td>
<td>43</td>
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