



agence d'évaluation de la recherche
et de l'enseignement supérieur

Research Units Department

AERES report on Unit:

Clinical epidemiology, mother and child health and
HIV in South East Asia

Under the supervision of the following
institutions:

Institut de Recherche pour le Développement (IRD)

Faculty of Associated Medical Sciences (AMS), Chiang
Mai University, Thailand

Harvard School of Public Health (not involved in the
future unit)

May 2012



agence d'évaluation de la recherche
et de l'enseignement supérieur

Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head

Pierre Glaudes



Unit

Name of unit:	UMI 174 - Clinical epidemiology, mother and child health and HIV in South East Asia
Acronym of unit:	
Label requested:	UMI 174 - Prevention and treatment of HIV infections and virus-associated cancers in South East Asia
Present no.:	
Name of Director (2009-2012):	Mr Marc LALLEMANT
Name of project leader (2013-2017):	Mr Gonzague JOURDAIN

Members of the committee of experts

Chair:	Ms Josiane WARSZAWSKI, Le Kremlin-Bicêtre
Experts:	Mr Prasert AUEWARAKUL, Bangkok, Thailand
	Mr Jean-François ETARD, Paris
	Ms Fatoumata OUATTARA-TRAORÉ, Marseille

Representatives present during the visit

Scientific Delegate representing AERES:

Ms Hélène GRANDJEAN

Representative(s) of the unit's supervising institutions and bodies:

Ms Régine LEFAIT-ROBIN, IRD representative in Thailand.

Mr Jakkapan SIRITHUNYALUG, CHIANG MAI UNIVERSITY

Mr Hervé TISSOT-DUPONT, IRD



Report

1 • Introduction

Date and conduct of the visit:

The visit to Chiang Mai took place on 15 and 16 May 2012, with J. WARSZAWSKI, J.F. ETARD as the delegates of the expert committee for both days and P. AUEWARAKUL as an additional delegate for the first day only.

On the first day, visits were conducted from 9 am to 3 pm, at three different sites: the virology and sample repository laboratory at Nong Hoi, the coordinating IRD-PHPT center and pharmacology and virology laboratories of the Faculty of Associated Medical Sciences (AMS), Chiang Mai University (CMU). At each site, the activities of the team members were presented. A videoconference was then held at the Information Technology Service Center (ITCS), CMU, between 3 and 6 pm, with the other member of the expert committee, Fatoumata Ouattara, and Helene GRANDJEAN, the AERES delegate, at the AERES office in Paris. After a general 15-minute overview by the proposed Director of the future unit, and a short exchange with the experts, six research subjects were presented successively by five researchers, interspersed with questions and discussions. A 30-minute closed meeting with PhD students and postdoctoral workers then took place with the on-site expert at the coordinating center.

On the second day, the two experts met with the Vice President for International Relations and Alumni Affairs of the University of Chiang Mai, in the presence of the Dean of the AMS and the Director of the future unit. Three other closed meetings with the expert committee were organized at the coordinating center, with: (i) the Director (1:30); (ii) 10 Thai members of the 85 technical and administrative staff able to speak English and involved in the management of various jobs or functions; (iii) the only permanent IRD "Ingenieur de recherche" (research officer).

The expert delegates held discussions on-site, in preparation for a telephone conference planned to take place after the visit.

History and geographic location of the unit, and overall description of its field and activities:

The international research group UMI 174 was established in 2005, through a tripartite agreement between IRD, France, the Faculty of Associated Medical Sciences, Chiang Mai University, Thailand and the Harvard School of Public Health, USA. The IRD-Program for HIV Prevention and Treatment (PHPT) has developed a clinical research platform, initially set up in 1996, including a network of 50 public hospitals across Thailand, a clinical trials unit (CTU) run by the IRD and based in Chiang Mai, for study design, administration and coordination and data management and analysis, and laboratories (molecular biology and pharmacology) dedicated to research on HIV and co-infections. These laboratories include the virology laboratory established at Nong Hoi, together with the sample repository, and virology and pharmacology laboratories established at the Faculty of Associated Medical Sciences (AMS) - Chiang Mai University.

The core activities of UMI 174 relate to the performance of clinical trials. The main objective over the last four years has been the development of strategies for optimizing the prevention of mother-to-child transmission of HIV (PMTCT), while minimizing the risk of selecting viral resistance to antiretroviral drugs. The secondary objectives over this period were: (1) to optimize care for HIV-infected adults and children, addressing critical operational and clinical questions, such as the optimal time/criteria for treatment switches, the clinical and immunological consequences of drug resistance, the pharmacology of antiretroviral drugs in specific populations, such as pregnant women and newborns, and the social and economic impact of treatment at the individual and community levels and (2) to develop research capabilities through the transfer of laboratory techniques and the implementation of quality systems, the training of healthcare providers, the establishment of community advisory boards and patients' networks and the promotion of higher education programs.

The PHPT made a major contribution to the decrease in mother-to-child transmission of HIV in Thailand and to improvements in the survival of infected patients. Clinical trials conducted by the UMI 174 have also contributed to the definition of international guidelines for PMTCT.

Several operational issues relating to access to care and long-term progression for HIV patients remain unresolved, but changes in the epidemiology of HIV justify the addition of research questions relating to other viral infections of major public health concern within South-East Asia, as proposed in the project for the new unit, with a renewal of the agreement between IRD, France, and AMS-CMU, Thailand.

The Harvard School of Public Health, USA, will not be an institutional partner in this new project.



Management team:

A two-party strategic management team is directed by an IRD researcher, the leader of the proposed new unit. The IRD party comprises the Unit Director from IRD, two Deputy Directors (one from IRD, the other from the Institut National des Etudes Démographiques (INED)) and one researcher from Harvard University. The AMS party comprises one Deputy Director from CMU, two CMU lecturers and one postdoctoral researcher.

The IRD team supervises five functional departments (clinical research implementation, social sciences, data processing, administration and finance, laboratory and pharmacology studies) at three sites in Chiang Mai (the coordinating center of the study for the four first departments, a virological laboratory in Nong Hoi, which houses the sample repository under the direct supervision of the IRD team, and pharmacological and virological laboratories at AMS).

Unit workforce:

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	0	0	
N2: EPST or EPIC researchers	3	2	2
N3: Other professors and researchers	12	14	8
N4: Engineers, technicians and administrative staff *on a permanent position	1	1	
N5: Engineers, technicians and administrative staff * on a non-permanent position	87***		
N6: Postdoctoral students having spent at least 12 months in the unit	1		
N7: Doctoral students	5		
N8: PhD defended	4		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	14	15	
TOTAL N1 to N7	109	17	10

* If different, indicate corresponding FTEs in brackets.

** Number of producers in the [01/01/2007-06/30/2011] period who will be present in 2013-2017.

Definition and downloading of criteria:

<http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation>.

*** This important staff from Chiang Mai University is still present in the new project



2 • Assessment of the unit

Overall opinion on the unit:

The research team has been responsible for some of the major randomized trials providing evidence for effective strategies for the prevention of mother-to-child transmission and contributing to the formulation of international guidelines.

The unit builds on the successful completion of several nationwide clinical trials, pathogenesis and socioeconomic studies, together with extensive training of healthcare providers and students. The results of the research trials conducted within this partnership have directly influenced the prevention and treatment of HIV in Thailand and worldwide, through the development of Thai and WHO guidelines, leading to a significant decrease in the risk of mother-to-child transmission of HIV, from 25% in the absence of intervention to less than 2% in formula-fed infants.

The team has carried out high-quality scientific work on issues of major importance to public health, with an obvious social utility for prevention of the mother-to child transmission of HIV transmission, both in Thailand and internationally.

The scientific project of the future unit will have a research remit extending beyond HIV, in line with the mission of the IRD, and encompassing other viral infections associated with cancers responsible for high levels of morbidity/mortality in the Greater Mekong Sub region. This development is relevant and logical and addresses new challenges for public health. However, for some of the new objectives proposed, specific questions remain to be more clearly defined and feasibility has yet to be demonstrated.

Strengths and opportunities:

The committee of experts has detected the following assets:

- High-quality scientific work, involving active collaboration between IRD researchers and members of Chiang Mai University;
- Direct impact of scientific results on the definition of national and international guidelines for PMTCT;
- Opportunity to conduct an original project in the field of hepatitis B at the regional level;
- Transfer of skills (in clinical research) and technology (in virology, molecular biology and pharmacology) to Thai healthcare professionals, through strong and stable local integration of the unit;
- Existence of a well structured, active, efficient clinical trials center, with certified quality procedures and training, involving a network of 50 clinical sites throughout Thailand, and a large, local technical staff capable of designing innovative projects and participating in international collaborative multicenter studies and trials.
- High potential to obtain funding.

Weaknesses and risks:

The committee of experts has made the following observations:

- The unit hosts a small number of permanent researchers and research officers from the IRD. Nevertheless, the scientific productivity of individuals, together with the investment of members from the other party (Chiang Mai University), has already proved effective for the performance of high-quality research;
- Specific questions remain to be defined and feasibility to be demonstrated for some of the new objectives proposed concerning HPV and HCV infections, economical issues, and retrospective analyses of the rich database and samples collected in clinical studies.



Recommendations:

The committee of experts makes the following recommendations:

- Improvements to governance through the establishment of a Scientific Committee to discuss strategic and scientific choices and agendas;
- Strengthening of integration into French universities, particularly in the domain of public health, for the supervision of Masters and PhD students, possibly jointly with the University of Chiang Mai;
- Increase in the critical mass of permanent researchers, showing a clear priority for the recruitment of French or Foreign postdoctoral researchers, in epidemiology and social science;
- Development of new collaborations with external teams, to make best use of the large mass of data and biological material collected.
- Identification of academic partners and human resources outside Thailand for the development of active collaborations for regional research projects.



3 • Detailed assessments

Assessment of scientific quality and production:

Since 2007, the research activities of the unit have focused on important issues for perinatal HIV transmission and the care of infected children: 1) identification of factors associated with the perinatal transmission of HIV and co-infections, 2) methods for preventing resistance to nevirapine, which is used to prevent the mother-to-child transmission of HIV, 3) pharmacokinetics of antiretroviral drugs during pregnancy and in children. Other studies have concerned the switch to a second-line regimen based on antiretroviral treatment monitoring strategies (CD4 vs. VL), socioeconomic benefits for patients on antiretroviral treatment and development of an international HIV specific quality of life questionnaire.

Original results have been obtained and published in about a hundred publications in international peer-reviewed journals, including the highest ranking and best specialist journals. Almost half these publications have included at least one team member as the first (or joint first), last (or joint last) or corresponding author. Articles have been published in the following journals, in particular: N Engl J Med (2), CID (5), AIDS (4), JID (2), J Clin Microbiol (1), Virology (2), PLoS One (1), PLoS Clin Trials (1), PID (3) JAIDS (6), AIDS Res Hum Retroviruses (1), HIV Med (2), Soc Sci Med (1), Antiviral Therapy (3), Br J Clin Pharmacol (1), Antimicrob Agents Chemother (1), J Antimicrob Chemother (2), J Gen Virol (1), Talanta (1), Ther Drug Monit (1), Mol Cancer (1), Pharmacogenomics (1), Infect Genet Evol (2), Am J Clin Pathol (1), International J of Infectious Dis (1), Eur J Haematol (5), Br J Ophthalmol (1), AIDS Patient Care and STDS (1), Mol Cell Prob (1), Clin Exp Immunol (1).

In recent years, the team has also been actively involved in collaborative multicenter clinical trials, in which they have played a major, although probably less visible role than as project leader.

Assessment of the unit's integration into its environment:

The unit has established a long-standing (over 10 years) strong, stable contractual partnership with Chiang Mai University. Thai academics are included among the key-authors listed on a large proportion of scientific publications, highlighting the contribution of the team to local research activities.

The unit plays an important role in structuring clinical research at national level in Thailand, and has transferred technology for early HIV diagnosis in infants to the Faculty of Associated Medical Science, Chiang Mai University. Infants throughout Thailand now have access to this technology, through the universal health coverage system.

The research unit is also heavily involved in the on-going education of Thai health professional: in-house training for all collaborators of UMI 174, training in laboratory quality assurance, training in HIV medicine and clinical research for physicians, pharmacists, nurses and counsellors and an HIV medicine symposium every two years for the wider HIV community in Thailand and neighbouring countries.

Assessment of the research unit's reputation and drawing power:

The team has achieved broad international recognition and has a good reputation for its scientific output and expertise in PMTCT trials. It is also involved in several international collaborative multicenter trials (as part of the PENTA and IMPAACT networks).

The team has been successful in attracting young scientists from Thailand, France and other countries: since 2007, five international volunteers, and six postdoctoral workers and PhD students have been recruited. Two of the 4 PhD students who have since defended their theses will be involved in the future unit: one as an AMS lecturer and the other as a postdoctoral worker.

Members of the unit served as experts for the WHO, during the development of PMTCT guidelines. One member was invited to write an Editorial in the NEJM. Members of the unit also participate in steering/scientific committees: IMPAACT, TREAT Asia Network, Ministry of Public Health Resistance Committee, ANRS AC11: "HIV -non B resistance and viral quantification".

The team has been efficient in raising funds for its research projects, with more than 30 research contracts signed with nine different sponsors, excluding joint funding from the NIH, Chiang Mai University and IRD partners.



Harvard University will not be involved in the joint funding of the future unit, but a permanent researcher from this university will continue to work full-time within this unit.

The unit has received funding from the Global Funds for the procurement of ARV drugs and HIV tests, ensuring that studies are adequately supplied with drugs and tests. This is a real advantage from an operational standpoint and in terms of autonomy from the ministry of Health, but it requires the unit to invest heavily in logistics and regulatory aspects.

Assessment of the unit's governance and life:

The governance of the unit is complex, with a two-party strategic management team, location at several sites (IRD and AMS), direction by an IRD researcher, and organization into functional clinical research departments, with weekly coordination meetings at the IRD-PHPT office.

Interactions between researchers from the IRD and AMS are effective, thanks largely to the long-standing and stable partnership. However, there is no scientific committee for the discussion of strategic and scientific choices, collaborations and identification of the research priorities of the unit.

The IRD team has provided considerable assistance in terms of quality assessment, including ISO9001 Certification of the Clinical Research Unit and ISO15189 Accreditation of the Microbiology Laboratory. The team has developed user-friendly computer software for the display of individual patient data and graphs to facilitate the monitoring of the clinical and laboratory status of the patients. Training, repeated every two years, is mandatory for all collaborators and technical staff of UMI 174. Polyvalence and mobility within the various departments are encouraged.

Assessment of the strategy and 5-year project:

The proposed project, which relates not only to HIV but also to several other non-HIV viral infections in Thailand and neighbouring countries, is in line with the general objectives and missions of the IRD and AMS, and responds to new challenges for public health. Viral hepatitis and HPV are major cause of deaths from cancer in the Greater Mekong Sub region and new effective vaccines and treatments need to be evaluated in both the short and long term.

Risk-taking is moderate, mostly due to the need for more formal partnerships with neighbouring countries and the incomplete funding of future projects.

- The research project on the determinants and prevention of mother-to-child transmission of hepatitis B at regional level is of major interest and includes a randomized trial that will benefit from the considerable expertise of the team in clinical research as applied to PMTCT.

- A PEERS (Programs of Excellence for Education and Research in South Countries) grant has recently been approved to support an original project concerning the neutralization of HIV, HBV and HCV by antibodies in the mother-to-child transmission context, coordinated by both UMI 174 and UMR U966, already involved in previous collaborations.

- The TEEWA multicenter study is an original social science research project aiming to evaluate life experiences of adolescents born with HIV and their integration into society. This study is of great interest because this population is increasing in size due to improvements in the survival of HIV-infected children, and the living conditions of these individuals and their long-term prognosis are largely unknown.

Specific research questions, feasibility and priorities, as a function of human and financial resources, need to be determined in greater precision for several other parts of the projects, particular as concerns: retrospective analyses of the rich database and samples collected from more than 1700 adults and 700 children on antiretroviral treatment in clinical studies since 2000; HPV and HCV infections; economic studies, which may benefit from collaborations with researchers in economics, not currently represented in the research unit, and social sciences.

Assessment of the unit's involvement in training:

IRD researchers have little involvement in academic teaching programs for Bachelor's or Masters degrees or through doctoral schools. Conversely, the AMS partners devote a large portion of their time to teaching undergraduate students, at the expense research activities.



Since 2007, five Masters dissertations and four PhD theses have been defended with at least two first-author publications. One of these former PhD students will join the future unit as an AMS lecturer and another has been recruited as an IRD postdoctoral worker. Four PhD students from French, British and Thai universities are currently supervised by members of the unit, with funding from various sources (ANRS, IRD, INED, London School of Hygiene and Tropical Medicine).



4 • Grading

Once the visits for the 2011-2012 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).

This score (A+, A, B, C) concerned each of the four criteria defined by the AERES and was given along with an overall assessment.

With respect to this score, the research unit concerned by this report (and, when necessary, its in-house teams) received the overall assessment and the following grades:

Overall assessment of the unit « UMI 174 - Clinical epidemiology, mother and child health and HIV in South East Asia » :

Unité dont la production et le rayonnement sont excellents. L'organisation, l'animation et le projet sont très bons.

Grading table:

C1	C2	C3	C4
Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
A+	A+	A	A



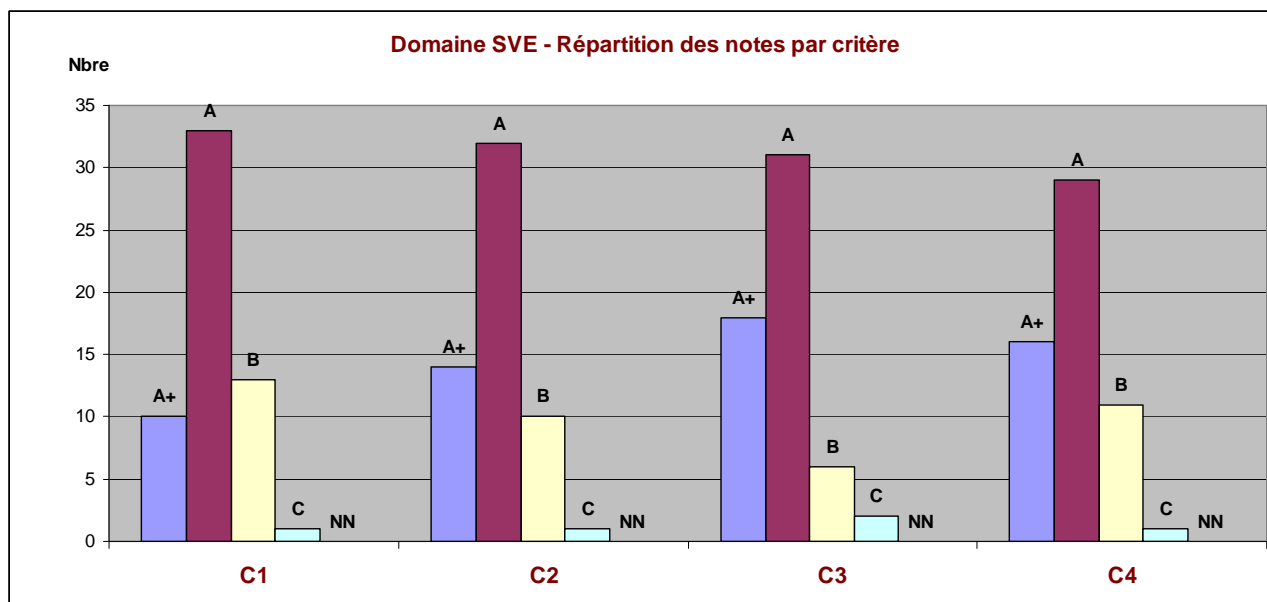
5 • Statistics per field

Notes

Critères	C1	C2	C3	C4
	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Gouvernance et vie du laboratoire	Stratégie et projet scientifique
A+	10	14	18	16
A	33	32	31	29
B	13	10	6	11
C	1	1	2	1
Non noté	-	-	-	-

Pourcentages

Critères	C1	C2	C3	C4
	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Gouvernance et vie du laboratoire	Stratégie et projet scientifique
A+	18%	25%	32%	28%
A	58%	56%	54%	51%
B	23%	18%	11%	19%
C	2%	2%	4%	2%
Non noté	-	-	-	-





6 • Supervising bodies' general comments



Institut de recherche
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AERES

REF : S2SF130004963 - UMI 174 Epidémiologie clinique, santé mère-enfant et VIH en Asie du Sud Est - 0133973Y

Marseille, le 28 juin 2012

Cher Monsieur,

Au nom de Michel Laurent, Président de l'IRD, de Pongsak Angkasith, Président de l'Université de Chiang Mai, de Wasna Sirinungsi, Doyenne de la Faculté de Sciences Médicales Associées de l'Université de Chiang Mai, et de l'ensemble des membres de l'UMI 174 PHPT, je tiens à remercier les membres du comité pour l'évaluation qui a été conduite par Josiane Warszawski, et pour le rapport qui en a été fait. Nous avons également particulièrement apprécié l'effort de l'AERES de dépêcher une partie du comité à Chiang Mai afin d'apprécier en toute objectivité le travail de cette unité.

*Agir avec le Sud
Acting with the South*

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Après relecture attentive de rapport, nous prenons acte des commentaires et recommandations contenues dans le rapport dont nous saurons tenir compte lors du renouvellement de cette unité de recherche.

La collaboration avec l'Université de Harvard est, et restera tout à fait active et productive, même si le projet d'unité ne prévoit plus que cette université soit une des tutelles officielles.

Enfin, à titre d'information et dans le cadre de l'extension thématique de l'UMI, je souhaitais également porter à la connaissance du comité que le projet d'essai clinique sur la prévention de la transmission périnatale du virus de l'hépatite B a été financé par le National Institute of Child Health and Development (NICHD) et les Centers for Diseases Control and Prevention (CDC) pour un montant de 1 857 000 US\$.

Très cordialement

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Institut de recherche
pour le développement

Mr Pierre GLAUDES
Director – Research Units Section
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REF : S2SF130004963 - UMI 174 Epidémiologie clinique, santé mère-enfant et VIH en Asie du Sud Est - 0133973Y

Marseille, june 26th, 2012.

Dear Mr Glaudes,

On behalf of Michel Laurent, President of the IRD, Pongsak Angkasith, President of Chiang Mai University, Wasna Sirinungsi, Dean of the Faculty of Associated Medical Sciences, Chiang Mai University, and the whole staff of UMI 174 PHPT, I do wish to thank the members of the experts committee for the evaluation visit led by Josiane Warszawski, and for their report. We do appreciate the effort of AERES to send some members of the committee to Chiang Mai in order to evaluate as objectively as possible the research conducted in this unit.

Agir avec le Sud
Acting with the South

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After careful review of the report, we take note of comments and recommendations which we will take into account upon renewal of this research unit.

The collaboration with Harvard University is and will remain quite active and productive, even if the proposed unit no longer provides this university as an official supervising institution.

Finally, for information purposes and as part of the thematic extension of the UMI, I also wanted to inform the committee that the proposed clinical trial on prevention of perinatal transmission of hepatitis B was recently funded by the National Institute of Child Health and Development (NICHD) and the Centers for Diseases Control and Prevention (CDC) for an amount 1,857,000 US\$.

Very sincerely

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