Annual Report

2018

NCGM-BMH
Medical Collaboration Center

February 2019
Tokyo, Japan-Hanoi, Viet Nam

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Preface

The collaboration between Vietnam and Japan through Medical Collaboration Center (MCC) in Bach Mai Hospital (BMH) becomes wide ranging, recently.

We, National Center for Global Health and Medicine (NCGM) are sending our staff to some projects in Vietnam, such as JICA projects on Nursing education and one for Cho Ray Hospital (CRH), and non-JICA projects for BMH and others that are relating directly to NCGM. These activities can be done based on not only JICA funds, but also several research funds, funding scheme for training by the Ministry of Health, Labour and Welfare, Japan, and so on.

In BMH, the new approach is going on. That is, not focusing on several individual specialties separately, but focusing on a team to cover several specialties for strengthening the service series of certain medical field, such as neurosurgery and related capacities including anesthesia, nursing, rehabilitation, pharmacy, and nutrition. Consequently, we are expecting that team care will be enhanced in BMH. In addition, some spin-off activities such as clinical application of food supplement was introduced.

The situations are changing rapidly, and we, NCGM, would like to continue to support the health sector of Vietnam. I believe that the MCC in BMH is the key and I hope the further collaboration will be happened between us in next year as well.

February, 2019

Hidechika Akashi, MD, PhD, MPH, DTMH
Director,
Medical Collaboration Center (MCC)
National Center for Global Health and Medicine (NCGM), Japan

Abbreviations

BMH	Bach Mai Hospital
NCGM	National Center for Global Health and Medicine
IMCJ	International Medical Center of Japan
MCC	NCGM - BMH Medical Collaboration Center
MOH	Ministry of Health, Viet Nam
AMED	Japan Agency for Medical Research and Development
MEXT	Ministry of Education, Culture, Sport, Science and Technology, Japan
J-GRID	Japan Initiative for Global Research Network on Infectious Diseases
MHLW	Ministry of Health, Labor and Welfare, Japan
JICA	Japan International Cooperation Agency
MOU	Memorandum of Understanding
HCMC	Ho Chi Minh City
NIHE	National Institute of Hygiene and Epidemiology
NHP	National Hospital of Pediatrics
NLH	National Lung Hospital
HLH	Hanoi Lung Hospital
RIT-JATA	Research Institute of Tuberculosis-Japan Anti-Tuberculosis Association
WHO	World Health Organization
JFPIMRC	Japan Foundation for the Promotion of International Medical Research Cooperation
SARS	Severe Acute Respiratory Syndrome
DCC	Disease Control and Prevention Center of NCGM

Contents

I. General information on NCGM-BMH Medical Collaboration Center (MCC)

1. Background

Since the beginning of 1990's, National Center for Global Health and Medicine (NCGM) (former IMCJ) has been carrying out important roles in collaboration with health sector in Vietnam for the purpose of the improvement of medical situation in the country. Particularly, collaboration with Bach Mai Hospital (BMH) has been implemented most actively and effectively. In the grant-aid and the technical cooperation projects in BMH, which was supported by Japan International Cooperation Agency (JICA), NCGM contributed to the successful implementation by dispatching experts and providing technical guidance.

Through the history of the past collaboration, NCGM has established close and reliable relationship with BMH and other leading medical institutions in Vietnam. Using these bases, a new collaboration, which was conducted distinctly from ODA projects and focusing on research and human resource development, was designed.

In order to implement the new collaborative activities, the NCGM-BMH Medical Collaboration Center (MCC) was planed.

2. Establishment of MCC

In view of the successful outcome of BMH project (phase 1) and the efficient collaboration during the SARS outbreak in 2003, a plan to establish a medical collaboration center between NCGM and BMH, which functions separately from JICA projects, grew up in NCGM. The idea was put into practice when the research program on emerging and reemerging infectious diseases was proposed by the Ministry of Education, Culture, Sports, Science and Technology, Japan (MEXT).

In recent years, emerging and reemerging infectious diseases have been threatening the world. In view of the rising fear of these diseases, the MEXT launched a new project in world-wide scale to cope with emerging and reemerging infectious diseases efficiently by setting up medical collaboration centers and conducting

close collaboration there. The proposal of the MEXT project facilitated the realization of MCC in Vietnam. After several preliminary studies, NCGM and BMH decided to establish MCC within BMH based on the friendly and reliable relationship, which had been developed since the beginning of 1990's between the two medical institutions.

The Memorandum of Understanding (MOU) regarding the initiation of the project was signed by the Director of BMH and the President of NCGM in August 2005 followed by the official approval of the Ministry of Health, Vietnam. In April 2010, NCGM changed its name (from International Medical Center of Japan; IMCJ to National Center for Global Health and Medicine; NCGM) due to its organizational reform (Independent Administrative Legal Entity). In view of this situation, both sides agreed to revise the MOU along with continuation of the current cooperative activities. After discussions between NCGM and BMH the revised MOU was drafted. In the new MOU, activities in MCC are clarified as research, training, medical case conferences, technical cooperation, international conferences/ meetings/ seminars, personal exchange programs, and others, although in the current version description of activity is concentrated on researches. The new MOU, after getting approval of MOH, was signed by the representatives of BMH (Dr. Nguyen Quoc Anh) and NCGM (Dr. Takaaki Kirino) in June 2, 2010.

Signing ceremony of the Memorandum of Understanding between NCGM and BMH in 2010

MCC office was established in the new building of BMH, which was constructed by Japan's grant-aid in 2000, as the managing center of various collaborative activities including the MEXT project and others.

Based on the MCC, various activities were started in collaboration with BMH along with related medical institutions.

3. Objective of MCC

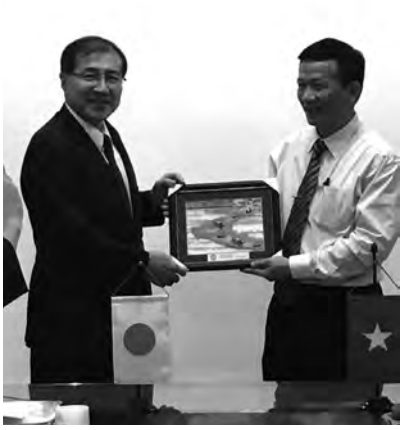
The objective of setting up MCC in Vietnam is to implement various collaboration on medical science and medical care, such as researches,

human resource development & technical exchange, information sharing, clinical case conference, etc. smoothly and effectively. The activities in MCC are conducted in close collaboration between BMH and NCGM, and related medical institutions and such collaborative activities are expected to benefit both Vietnam and Japan. The contents of activities can include some advanced and sophisticated techniques, which had been difficult to conduct within the framework of JICA projects.

4. Related medical institutions

MCC is mainly collaborating with BMH, however based on the agreement described in MOU; some related medical institutions have been setting up under the approval of BMH.

Currently, five institutions in Hanoi and three institutions in Ho Chi Minh City are functioning as the main related medical institutions. In the future, more medical institutions might be added if necessary and efficient network building among them of is expected.



NCGM President, Dr. Norihiro Kokudo visited BMH on Jun 25, 2018

Table 1: Main medical institutions under collaboration (As of December 2018)

No.	Medical institution	Location	Collaborative study
1	National Institute of Tropical and Infectious Diseases	Hanoi	HIV/AIDS
2	National Lung Hospital (the former National Hospital of Tuberculosis and Lung Diseases)	Hanoi	Tuberculosis
3	Hanoi Lung Hospital (the former Hanoi Hospital of Tuberculosis and Lung Diseases)	Hanoi	Tuberculosis
4	Cho Ray hospital	HCMC	Healthcare associated
5	Ho Chi Minh Medical and Pharmaceutical University	HCMC	Tropical Medicine
6	Ho Chi Minh City Hospital of Tropical Medicine	HCMC	Tropical Medicine Medical education
7	National Institute of Nutrition	Hanoi	Diabetes and life style related disease

5. MEXT's program

The Ministry of Education, Culture, Sports, Science and Technology, Japan (MEXT) is implementing the MEXT "Program of Founding Research Centers for Emerging and Reemerging Infectious Diseases" in Asian and African countries. The objective of these activities is to contribute to the emerging infectious diseases and other disease control from the world-wide viewpoint. As of December 2008, this program has been implemented in 11 research centers in 8 countries (Vietnam, China, India, Thailand, Indonesia, Zambia, Ghana, Philippines). MCC is functioning as one of the important research centers for this program in Vietnam. The period of this program is 5 years from April 2005 to March 2010. The next step started from April 2010 to March 2015, and now the third step has been started from April 2015.

Currently, the projects supported by MEXT account for the major part of the activities of MCC. Activities of the MEXT projects in Vietnam include scientific researches (both basic and clinical researches), human resource development, etc. Equipment necessary for conducting these activities has also been provided to BMH and relevant medical institutions.

MEXT's program in Vietnam consists of the following three research groups (Dr. Shinichi Oka is the leader of these researches). These groups are implementing activities on emerging and reemerging infectious disease control based on the concept of MEXT project. The following three researches are three leading research subjects in MCC and under these research themes, sub-researches have been carried out.

1) Dr. Shinichi Oka's group: HIV/AIDS
2) Dr. Norio Ohmagari's group: Bacterial infections
3) Dr. Naoto Keicho's group: Tuberculosis

6. The program for international promotion of Japan's healthcare technologies and services

The program has been started from 2015, organized by the Bureau of International Health Cooperation and relevant departments of NCGM and funded by the Ministry of Health, Labour and Welfare, Japan. This program is in relation to the Memorandum of Cooperation in the field of healhcare between the Ministry of Health, Labour and Welfare of Japan and the Ministry of Health of Vietnam signed on 18 March 2014 by both Ministers. This program aims at carrying out the major objectives of promotion, including sharing the experiences in Japan's public health insurance system and the transfer of cutting-edge medical technologies. Through this program, public health standards in the counterpart countries will be improved.

Under this program, in the year 2018, fifteen staff members of BMH were invited to NCGM for training in different fields, such as neurosurgery, stroke care including rehabilitation, nutrition, and pharmacy; peri-operative care including intensive care and anesthesiology; and medical equipment management. Besides

that, eight staff members from other hospitals in Vietnam were also invited to NCGM for training in hospital quality management on nursing. Thirty-three experts from NCGM also came to BMH for investigating the needs, discussing the contents of training and collaborative activities, as well as following-up the implementation in BMH after training courses and assessing the outcome. This program is highly evaluated by BMH, contributing to provide better healthcare services to more people in Vietnam.

The NCGM stroke care team headed by Dr. Tetsuo Hara, Vice Director of Center hospital, NCGM, working with BMH in Jun 2018

This Program has been extended to Cho Ray hospital and initial steps for preparation have been done in the year 2018. It is expected that more people in the south of Vietnam can be benificiary from this Program, through the enhancement of healthcare service in Cho Ray hospital.

7. Other projects

In addition to the obove, the Ministry of Health, Labor and Welfare of Japan (MHLW) is also supporting research projects on various fields. As an oversea base of NCGM, MCC is functioning as a body to support NCGM research teams or individuals who want to implement a collaborative project in Vietnam.

Within this scope, life-style related diseases such as diabetes and pediatric health issues are projects which have been implemented in collaboration with BMH and other medical institutions of Vietnam so far. A community-based suvery on diabetes and obesity, followed by an intervention program has been implementing in Hanoi area and a lot of meaningful data have been obtained with the support from MCC.

8. Current MCC

MCC received many groups of researchers and specialists coming from NCGM and related institutions in Japan. MCC staff participated in discussions on related activities held between the two sides. Together with Vietnamese counterparts, MCC staff took part in conducting, supervising and monitoring on-site implementation of researches, as well as collecting and reporting data. In addition to that, MCC has provided logistic support to these groups, such as on-site coordination including making appointments with Vietnamese counterparts, reservation of accommodation, arrangement of transportation vehicles etc.

In 2018, MCC also participated in arrangement of the training visits for NCGM trainees. Trainee groups

including doctors, nurses, technicians, and pharmacists came to BMH and other hospitals and healthcare centers in Hoa Binh province for the training on global health and medicine.

MCC staff also supported administrative procedures for Vietnamese counterparts, who were invited to Japan for training. In 2018, 23 counterpart members have completed necessary procedures and successfully received training in Japan. Through this activity, MCC also acts as a bridge to link domestic health personnel and institutions, which is necessary for sustainable improvement.

II. Activities

1. Research

List of collaborative researches in MCC, Viet Nam

Table 2 : Collaborative researches in MCC, Viet Nam

No.	Main Researchers	Affiliation in Viet Nam	Subject	Source of fund
1	Shinichi Oka (NCGM)	National Hospital of Tropical Diseases (NHTD) Bach Mai Hospital (BMH)	The cohort study of HIV-1-infected individuals in Northern Viet Nam	AMED
2	Kajio Hiroshi (NCGM) Pham Minh Thong (BMH) Nguyen Khoa Dieu Van (BMH)	Bach Mai Hospital (BMH)	Study on the contribution of obesity to diabetes and blood vascular diseases in Viet Nam	NCGM MHLW
3	Kajio Hiroshi (NCGM) Nguyen Quoc Anh (BMH) Dinh Thi Kim Lien (BMH)	Bach Mai Hospital (BMH)	Impact of a life style intervention in incident and prevalence of overweight and obesity among secondary school children in Hanoi	NCGM MHLW
4	Norio Ohmagari (NCGM) Nguyen Quoc Anh (BMH) Pham Thi Ngoc Thao (CRH)	Bach Mai Hospital (BMH) Cho Ray Hospital (CRH)	Research on Epidemiology, Diagnosis and Treatment for Healthcare Associated Infection and Antimicrobial Resistant Bacteria in Vietnam	J-GRID AMED
5	Tohru Miyoshi-Akiyama (NCGM)	Bach Mai Hospital (BMH)	Emergence and Spread of Epidemic Multidrug-Resistant *Pseudomonas aeruginosa*	J-GRID AMED
6	Fumihiko Hinoshita (NCGM) Do Gia Tuyen (BMH)	Bach Mai Hospital (BMH)	Sister Renal Center Program, International Society of Nephrology	ISN
7	Naoto Keicho (NCGM/JATA) Pham Huu Thuong (HLH)	Hanoi Lung Hospital (HLH) National Lung Hospital (NLH)	Research on tuberculosis in Viet Nam, Research on spreading Beijing-genotype strains of *Mycobacterium tuberculosis*, their drug-resistance profiles and possible effects on treatment outcome	J-GRID AMED
8	Naoto Keicho (NCGM/JATA) Pham Huu Thuong (HLH)	Hanoi Lung Hospital (HLH)	Research on latent tuberculosis infection among healthcare workers in Hanoi, Vietnam	AMED
9	Hiroyuki Shichino (NCGM)	National Hue Central Hospital (Hue) Ho Chi Minh Children Hospital 1 (HCM city) Ho Chi Minh Children Hospital 2 (HCM city) Ho Chi Minh Children Hospital 3 (HCM city) National Hospital of Pediatrics (Hanoi) National Cancer Hospital (Hanoi)	Support for Strengthening Medical Treatment Ability of the Childhood Cancer in Viet Nam	NCGM MHLW

Research No.1

1.	**Title(in English)**	The cohort study of HIV-1-infected individuals in Northern Viet Nam
2.	**Title(in Japanese)**	ハノイにおける HIV 感染者のコホート研究
3.	**Main researcher**	Shinichi Oka (AIDS Clinical Center, National Center for Global Health and Medicine, Japan)
4.	**Co-Researcher(s)**	Junko Tanuma, Daisuke Mizushima, Hiroyuki Gatanaga, Shoko Matsumoto, Mika Sata, Ei Kinai, Masafumi Takiguchi, Nguyen Thi Huyen, Nguyen Hoai Dung, Tran Van Giang, Nguyen Vu Trung, Nguyen Van Kinh, Truong Thai Phuong, Doan Thu Tra, Do Duy Cuong
5.	**Resource of fund**	Japan Agency for Medical Research and Development (AMED)
6.	**Affiliation(s) in Viet Nam**	National Hospital of Tropical Diseases (NHTD) Bach Mai Hospital (BMH)
7.	**Period of the research**	October 2007- March 2020
8.	**Publications**	1. D. Mizushima et al. ***J Infect Chemother***. 2018 Jul;24(7).

9. **Summary:**

In 2007, we established a hospital-based cohort of HIV-infected individuals in Hanoi, Viet Nam under the Japan Initiative for Global Research Network on Infectious Diseases (J-GRID) network, which aimed to enhance the research collaboration on HIV between Japan and Viet Nam. We recruited participants in both the National Hospital for Tropical Diseases (NHTD) and Bach Mai Hospital (BMH) in urban Hanoi and 2,198 HIV-infected individuals have joined the cohort by the end of 2018. Data on demographics, clinical status and laboratory data has been prospectively collected every year and it has now become the longest clinical dataset of HIV-infected patients in Northern Viet Nam. ARV success rate has been almost as high as Japan in this cohort.

Using the HIV cohort, we evaluated ARV-induced tubular dysfunction (TD) and chronic kidney diseases (CKD) in a total of 1,382 participants. TD was defined as urinary beta 2 microglobulin (β2MG) > 1000 μg/L at two time-points or increase in β2MG by > 2000 μg/L. Chronic kidney disease (CKD) was defined as creatinine clearance ≤60 ml/min or urinary protein/creatinine ratio ≥ 0.15 g/gCre at two time-points. Among the participants, 41.5% were female; 98.2% were on ART, 76.3% were on tenofovir (TDF); 22.4% had never TDF exposure. TD and CKD were diagnosed in 13% and 8.3% of all patients, respectively. In multivariate analyses, age (OR = 1.057; 95%CI, 1.034-1.081), being female (OR = 0.377; 95%CI, 0.221-0.645), HBsAg positive (OR = 1.812; 95%CI, 1.134-2.894), HCVAb positive (OR = 1.703; 95%CI, 1.100-2.635), TDF exposure (OR = 9.226; 95%CI, 2.847-29.901) and ritonavir boosted lopinavir (LPV/r) exposure (OR = 5.548; 95%CI, 3.313-9.293) were significantly associated with TD. Moreover, age (OR = 1.093; 95%CI, 1.068-1.119), being female (OR = 0.510; 95%CI, 0.295-0.880), weight (OR = 0.909; 95%CI, 0.879-0.939), hypertension (OR = 3.027; 95%CI, 1.714-5.347), TDF exposure (OR = 1.963; 95%CI, 1.027-3.7 53) and LPV/r exposure (OR = 3.122; 95%CI, 1.710-5.699) were significantly associated with CKD. In conclusion, TDF and LPV/r exposure were strongly associated with TD and CKD, in addition to their known risks. Therefore, this study implied that we need to pay more attention to renal safety for patients on second line ART.

Recently, with economic growth of Vietnam, HIV treatment financial base has rapidly delegated from foreign aids to Vietnamese health insurance system. Under the health insurance, patients expected to bear copayment for HIV services and to be treated at registered local clinics. Co-payment would be conducive to decline of ART adherence, since HIV-infected individuals generally avoid seeking HIV services at local clinics, being afraid of their HIV status disclosed.

In this transitional period of Vietnamese HIV policy, we need to closely monitor the effectiveness of ART and other impacts of policy transition using our strong research foundation established in Viet Nam.

Other currently active researches include;

1) prevalence of drug resistance among those failing ART

2) incidence of adverse effects against ART

3) prevalence of rickets among children born from mothers receiving ART

4) quality of life measurement by the WHOQOL and other indicators.

All of these studies will provide key information on the long-term prognosis of HIV-infected individuals in Viet Nam as well as offered a variety of opportunities for young investigators to work with colleagues from a different country in the field of HIV.

Research No.2

1	Title (in English)	Study on the contribution of obesity to diabetes and blood vascular diseases in Viet Nam
2	Title (in Japanese)	ベトナム人における肥満の糖尿病や心血管疾患への関与に関する研究
3	Main researcher	Kajio H (Director, Department of Diabetes, Endocrinology and Metabolism, NCGM, Japan) Pham MT (Vice Director, BMH, Vietnam) Nguyen KDV (Director, Department of Diabetes and Endocrinology, BMH, Vietnam)
4	Co-Researcher(s)	Japan: Matsushita Y (NCGM), Tsujimoto T(NCGM) Viet Nam: Do DL (BMH), Nguyen PA (BMH), Thuy PTP (MCC)
5	Resource of fund	1. The Grant of National Center for Global Health and Medicine, NCGM, Japan 2. The Grant of Ministry of Health, Labor and Welfare of Japan
6	Affiliation(s) in Viet Nam	Bach Mai Hospital
7	Period of the research	May 2011-
8	Publications	None
9	Summary:	

Obesity is supposed to contributing to the deterioration of metabolic abnormalities for diabetes and cardiovascular diseases (CVD). Intra-abdominal adipose tissues (VATs) secret bioactive hormones and partially regulate the functions of insulin-sensitive organs as well as the vascular functions. The amounts of these hormones are largely dependent on the degree of fat accumulation in VAT. The visceral fat area (VFA) determined using CT or MRI was a superior predictor for the clustering of metabolic risk factors. CT and MRI are not simple or cost-effective, and often unsuitable for screening large number of participants. CT has a problem with X-ray exposure. Recently, several apparatus for the direct measurement have been developed based on the bioelectrical impedance analysis (BIA). The advantages of BIA include its portability and ease of use, relatively low cost, minimal participant participation required, and safety (not for participants with a pacemaker), thus making it attractive for large-scale studies.

The aims of our study are to establish a system based on abdominal BIA by comparing with the result of CT scan, and to identify directly the association of obesity, especially visceral obesity, and diabetes and blood vascular diseases.

We started the recruitment of 300 (150 males, 150 females) participants at Bach Mai Hospital. in 2016. At the moment, we have recruited 287 subjects. The characteristics of the subjects are shown below.

Gender: 146 males, 141 females / Age: 131 (<50 years old), 156 (>= 50 years old) / BMI: 149 (<23), 138 (>= 23) /
Blood pressure: 90 (<120/80), 188 (120/80 - 140/90), 9 (>140/90)

No	Variables		Normal	Abnormal
1	Glucose (mmol/L)	(4-6)	113	174
2	HbA1c (%)	(4-6)	99	188
3	Insulin (uU/mL)	(2.6-24.9)	146	41
4	Creatinin (μmol/L)	(59-104)	202	84
5	AST (U/L)	(<37)	264	23
6	ALT (U/L)	(<41)	247	40
7	CRP (mg/dL)	(<0.5)	254	30
8	Cholesterol (mmol/L)	(<5.2)	195	92
9	Triglyceride (mmol/L)	(2.26)	197	89
10	HDL (mmol/L)	(≥ 1.45)	66	220
11	LDL (mmol/L)	(≤ 3.4)	231	56
12	ECG		273	12
13	L-ABI	(0.9-1.4)	278	8
14	VFA-male	(<90m2)	38	108
15	VFA-female	(<80m2)	62	79

We will almost finish the recruitment, and start the evaluation of the data to clarify the association of obesity, especially visceral obesity, and diabetes and blood vascular diseases in Vietnamese people.

Research No.3

1	Title (in English)	Impact of a life style intervention in incident and prevalence of overweight and obesity among secondary school children in Hanoi
2	Title (in Japanese)	ハノイ市の中学生における肥満・過体重に対する生活習慣介入に関する研究
3	Main researcher	Kajio H (Department of Diabetes, Endocrinology and Metabolism, NCGM, Japan) Anh NQ (BMH, Viet Nam) Lien DTK (Center of Nutrition, BMH, Vietnam)
4	Co-Researcher(s)	Japan: Matsushita Y (NCGM), Tsujimoto T(NCGM), Hara M (Tokyo Metropolitan Hiroo General Hospital) Viet Nam: Thanh DVT (BMH), Thanh NTT (BMH), Thuy PTP (MCC)
5	Resource of fund	1. The Grant of National Center for Global Health and Medicine, NCGM, Japan 2. The Grant of Ministry of Health, Labor and Welfare of Japan
6	Affiliation(s) in Viet Nam	Bach Mai Hospital
7	Period of the research	Dec 2012-
8	Publications	In Preparation
9	Summary:	

In the developing countries, the increasing prevalence and incidence of overweight and obesity is a serious public health problem induced by the social and economic changes of the countries. The prevalence has increased at an alarming rate also in children. Overweight and obese children are likely to stay obese into adulthood and more likely to develop non-communicable diseases (NCD) like diabetes and cardiovascular diseases at a younger age. We performed the study on the impact of a life style intervention against overweight and obesity among secondary school children in Hanoi from 2012 to 2016.

We recruited 821 children of 6th grade from 4 different schools Cat Linh school Nguyen Cong Tru School Phan Chu Trinh School Dong Da school , which were randomly selected from 2 urban districts in Hanoi. After allocation of 4 schools into two groups, two schools for the intervention group and the other two schools for the control group, we performed intervention activities for two years. We provided the participants with the pedometers, and the participants in the intervention group were also provided with the scales. As for the behavior intervention, we promoted the participants in the intervention group to continue the activities with self-monitoring, goal setting, and problem solving. The analysis of the results is now being performed. We obtained the baseline data from 821 children of 4 schools.

We found high prevalence of overweight and obesity. Children of parents with college or university degree had the lowest risks for OW/OB. Children with a family history of OW/OB had an increased risk of OW/OB, especially the odds ratio of OW/OB for children significantly increased when one or both parents were OW/OB. Children with a birth weight of 3,500g or more had an increased risk of OW/OB. Obesity was positively associated with eating behaviors such as eating fried food and eating sub-meals. Children having specific positive lifestyle behaviors, such as weight-reducing exercises, lowered food intake or adding vegetables to their diet, had lower risks for OW/OB.

The results suggested that children with OW/OB parents or a high birth weight should be educated to prevent OW/OB at an early stage. The results also suggested that education for parents might be associated with OW/OB among children. To reduce the prevalence of OW/OB among children, it is recommended that the students should be facilitated toward positive eating and lifestyle behaviors such as weight-reducing exercises, lowered food intake, and adding vegetables to the diet. We have already reported part of the results at several scientific meetings. And, we will have a presentation at Nutrition and Metabolism Panel of U.S.-Japan Cooperative Medical Sciences Program (USJCMSP) 21st International Conference on Emerging Infectious Diseases in The Pacific Rim, which will be held in Hanoi on February 28, 2019.

We revealed the high prevalence of overweight or obesity in school children, and several factors influencing on the appearance of overweight or obesity. It is very important to identify the factors related to the behavioral changes of the students and their parents through the intervention introducing the reduction of the prevalence and incident of overweight and obesity in the children. We are now continuing the analyses of the important topics. These analyses would help us make the strategy for the intervention of NCD.

Research No.4

1	Title (in English)	Research on Epidemiology, Diagnosis and Treatment for Healthcare Associated Infection and Antimicrobial Resistant Bacteria in Vietnam
2	Title (in Japanese)	ベトナム拠点における医療関連感染症及び抗菌薬耐性菌感染症に関する検討
3	Main researcher	Norio Ohmagari MD, MSc, PhD (Director, Disease Control and Prevention Center, National Center for Global Health and Medicine) Nguyen Quoc Anh MD., PhD. (Director, Bach Mai Hospital) Pham Thi Ngoc Thao (Vice Director, Cho Ray Hospital)
4	Co-Researcher(s)	Japan: Tohru Miyoshi-Akiyama, PhD (NCGM), Sho Saito, MD. (NCGM), Masahiro Ishikane, MD., PhD (NCGM), Kayoko Hayakawa, MD., PhD (NCGM), Satoshi Kutsuna, MD., PhD (NCGM), Maki Nagashima (NCGM), Pham Thi Phuong Thuy BA. MPH (NCGM-BMH Medical Coloration Center) Viet Nam: Prof.Nguyen Gia Binh, MD., PhD (BMH/Senior Advisor of ICU Dept.), Dao Xuan Co (BMH/Head of ICU Dept.), Truong Thai Phuong MD., PhD (BMH/Head of Microbiology Dept.), Do Van Thanh (BMH/Infectious Dept. and International Dept.), Pham Thi Ngoc Thao (Vice Director, Cho Ray Hospital), Phan Thi Xuan (Head of General ICU, Cho Ray Hospital), Hoang Lan Phuong (International Affairs, Cho Ray Hospital), Huynh Quang Dai (General ICU, Cho Ray Hospital), Nguyen Ly Minh Duy (General ICU, Cho Ray Hospital), Truong Thien Phu (Microbiology Dept, Cho Ray Hospital), Phung Manh Thang (Infection Control Department, Cho Ray Hospital)
5	Resource of fund	The Program of Japan Initiative for Global Research Network on Infectious Diseases (J-GRID), AMED
6	Affiliation(s) in Viet Nam	Bach Mai Hospital (BMH), Viet Nam Cho Ray Hospital (CRH), Viet Nam
7	Period of the research	April 1, 2012 to March, 2019
8	Publications	Jpn J Infect Dis. 2018 Oct 31. doi: 10.7883/yoken.JJID.2018.163. [Epub ahead of print]
9	Summary:	

1. Assessment of Bacteremia in a Large Tertiary Care Hospital in Northern Vietnam: A Single-center Retrospective Surveillance Study

Jpn J Infect Dis. 2018 Oct 31. doi: 10.7883/yoken.JJID.2018.163. [Epub ahead of print]

Takeshita N(1), Anh NQ(2), Phuong DM(3), Thanh DV(2), Thuy PP(4), Huong MTL(3), Takahashi M(1), Ohmagari N(1).

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The clinical analysis of cases of Bacteremia would be valuable. However, thus far, limited data on bacteremia are available in Vietnam. A single-center, retrospective surveillance study was conducted in Bach Mai Hospital, Hanoi, Vietnam from 2009 to 2012. In total, 45,366 blood culture cases were analyzed. The number of blood cultures per 1,000 patient-days was 9.59 sets. The percentage of solitary blood culture sets was 49.6%. The rate of positive blood culture was 13.9%. The major

pathogens isolated in adults were coagulase-negative Staphylococcus species (16.7%), followed by Escherichia coli (6.8%), Streptococcus spp. excluding Streptococcus pneumoniae (3.8%), and Staphylococcus aureus (5.2%). Other major pathogens were Klebsiella spp. (4.2%) and Acinetobacter spp. (2.2%). The number of blood cultures per 1,000 patient-days was lower and the percentage of solitary blood culture sets in the present study was higher than that of the Japanese study (9.6 vs. 25.2 and 49.6% vs. 32.8%). The distribution of microorganisms was unique in terms of the relative predominance of Acinetobacter cases. The percentage of cases of healthcare-associated bacteremia may be relatively high.

DOI: 10.7883/yoken.JJID.2018.163
PMID: 30381680

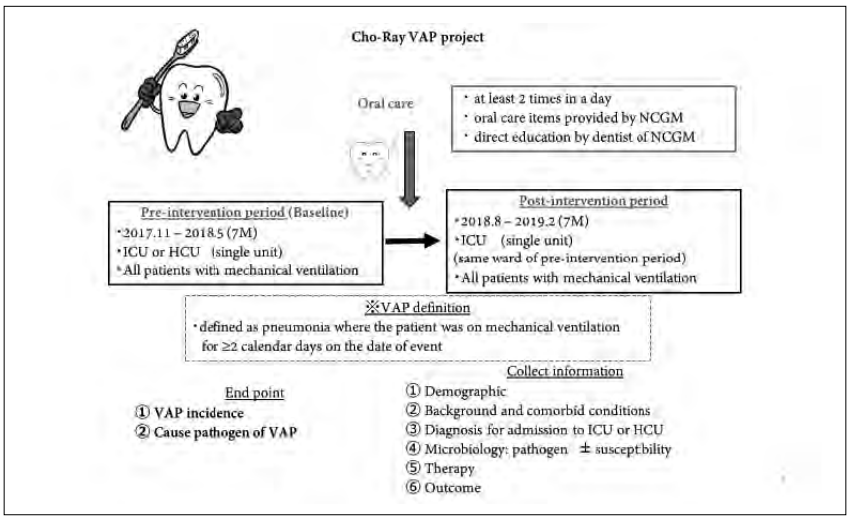
2. Oral Care

In a previous observation at Cho Ray Hospital(CRH), we discovered that nurses, instead of dentists, were performing oral care in the general ICU and the oral care process was not adequate. In this study, we provide instructions to local doctors and nurses in a new oral care protocol as an intervention. After the instruction, we evaluate the effects of the new oral care protocol in terms of the VAP cumulative incidence difference.

Pre intervention period (baseline); the oral care remains the same as the current standard oral care performed in the general ICU, and the patients are monitored for VAP; the cumulative incidence of VAP is calculated.

Oral care training period; dentists from NCGM specifically trained for the new oral care protocol will begin to instruct local doctors and nurses of the general ICU.

Post intervention period; patients are monitored for VAP, and the cumulative incidence of VAP is calculated. The quality of oral care will be evaluated based on the checklist for the new oral care protocol by doctors and nurses of CRH, and dentists of NCGM also periodically check the level of care.



Educational activities:

Training Course on Case Management of Tropical Infectious Diseases was held at Ho Chi Minh City, Vietnam (December 2018).

Research No.5

1	Title (in English)	Emergence and Spread of Epidemic Multidrug-Resistant *Pseudomonas aeruginosa.*
2	Title (in Japanese)	流行型多剤耐性緑膿菌の出現と拡散
3	Main researcher	Tohru Miyoshi-Akiyama (NCGM)
4	Co-Researcher(s)	Tatsuya Tada, Norio Ohmagari, Nguyen Viet Hung, Prasit Tharavichitkul, Bharat Mani Pokhrel, Marek Gniadkowski, Masahiro Shimojima, Teruo Kirikae
5	Resource of fund	AMED, J-GRID
6	Affiliation(s) in Viet Nam	Bach Mai Hospital
7	Period of the research	2012-2017
8	Publications	Genome Biol Evol. 2017 Dec; 9(12): 3238–3245
9	Summary:	

Pseudomonas aeruginosa (P. aeruginosa) is one of the most common nosocomial pathogens worldwide. Although the emergence of multidrug-resistant (MDR) *P. aeruginosa* is a critical problem in medical practice, the key features involved in the emergence and spread of MDR *P. aeruginosa* remain unknown. This study utilized whole genome sequence (WGS) analyses to define the population structure of 185 *P. aeruginosa* clinical isolates from several countries. Of these 185 isolates, 136 were categorized into sequence type (ST) 235, one of the most common types worldwide. Phylogenetic analysis showed that these isolates fell within seven subclades. Each subclade harbors characteristic drug resistance genes and a characteristic genetic background confined to a geographic location, suggesting that clonal expansion following antibiotic exposure is the driving force in generating the population structure of MDR *P. aeruginosa*. WGS analyses also showed that the substitution rate was markedly higher in ST235 MDR *P. aeruginosa* than in other strains. Notably, almost all ST235 isolates harbor the specific type IV secretion system and very few or none harbor the CRISPR/CAS system. These findings may help explain the mechanism underlying the emergence and spread of ST235 P. aeruginosa as the predominant MDR lineage.

Research No.6

1	Title (in English)	Sister Renal Center Program, International Society of Nephrology
2	Title (in Japanese)	国際腎臓学会 Sister Renal Center Program
3	Main researcher	Fumihiko Hinoshita (MD, Ph.D, Head, Department of Nephrology, NCGM) Do Gia Tuyen (MD, Ph D, Head, Department of Nephro-Urology, Bach Mai Hospital)
4	Co-Researcher(s)	Manami Tada (MD, Department of Nephrology, NCGM) Nguyen Thi Huong (MD, Department of Nephro-Urology, Bach Mai Hospital)
5	Resource of fund	Sister Renal Center Program funded by International Society of Nephrology (ISN)
6	Affiliation(s) in Viet Nam	Bach Mai Hospital
7	Period of the research	January 2014- December, 2019
8	Publications	None
9	Summary:	

OVERALL PURPOSE:

- To establish further collaboration between Dept of Nephrology, NCGM and Dept of Nephro-Urology, BMH under the Sister Renal Center Program officially approved by International Society of Nephrology (ISN)
- To establish a sophisticated means of treating patients with CKD in the preservation period and retard the progression of CKD in the patients in BMH as well as local hospitals in Northern Viet Nam
- To improve management of hemodialysis at BMH and the dialysis facilities in Hanoi

ACTIVITIES:

- Nephrologists from NCGM and BMH had lectures on “Renal Replacement Therapy and Hemodilalysis Initiation for Maintenance Hemodialysis in Japan ” and “Diagnosis and Strategy of Treatment of Glomerular Diseases in Japan” at BMH.
- Upgrading from Level B to Level A under the Sister Renal Center Program was officially approved by ISN in 2018 according to the good evaluation of the activities between NCGM and BMH. The status of Level A under the Sister Renal Center Program will continue for two years.
- A clinical research of “The clinical characteristics of the newly hemodialyzed patients with CKD at a major hospital of Hanoi, Viet Nam” is under progress at BMH under the Sister Renal Centers Program.

Research No.7

1	Title (in English)	Research on tuberculosis in Viet Nam Research on spreading Beijing-genotype strains of *Mycobacterium tuberculosis*, their drug-resistance profiles and possible effects on treatment outcome
2	Title (in Japanese)	ベトナムにおける結核症に関する研究 結核菌北京型株の蔓延と多剤耐性に関わる研究
3	Main researcher	Naoto Keicho (NCGM/Research Institute of Tuberculosis, JATA) Pham Huu Thuong (Hanoi Lung Hospital)
4	Co-Researcher(s)	Vu Cao Cuong (Hanoi Department of Health) Hoang Van Huan (Hanoi Lung Hospital) Nguyen Phuong Hoang (Hanoi Lung Hospital) Nguyen Van Hung (National Lung Hospital) Shinji Maeda (Hokkaido Pharmaceutical University School of Pharmacy) Minako Hijikata (NCGM/Research Institute of Tuberculosis, JATA) Nguyen Thi Le Hang (NCGM-BMH Medical Collaboration Center)
5	Resource of fund	The Program of Japan Initiative for Global Research Network on Infectious Diseases (J-GRID), AMED
6	Affiliation(s) in Viet Nam	Hanoi Lung Hospital (HLH), Viet Nam National Lung Hospital (NLH), Viet Nam
7	Period of the research	2015-2020
8	Publications	**Comparison between conventional genotypes and whole genome sequencing of *M. tuberculosis* isolated in Hanoi, Vietnam** Shinji Maeda, Ikumi Matsushita, Minako Hijikata, Naoto Keicho (non-member: Pham Huu Thuong, Nguyen Phuong Hoang, Nguyen Thi Le Hang, Vu Cao Cuong, Pham Thu Anh) Presented at the 93rd Annual Meeting The Japanese Society for Tuberculosis 2018/6/23-6/24 Osaka **Disease susceptibility to human mycobacterial infection** Naoto Keicho, Ikumi Matsushita, Shintaro Seto, Minako Hijikata, Shinji Maeda Presented at the 93rd Annual Meeting The Japanese Society for Tuberculosis 2018/6/23-6/24 Osaka **A role of genetic variants and expression of interleukin-12 receptor subunit beta2 in protection against tuberculosis** Minako Hijikata, Nahoko Kato-Kogoe, Nguyen Thi Le Hang, Do Bang Tam, Vu Cao Cuong, Pham Huu Thuong, Naoto Keicho Presented at the 49th union world conference on lung health TBScience2018 (Pre-conference) 2018/10/24-10/27 Den Haag, The Netherlands
9	Summary: **Overall purpose** • To strengthen collaborative research work on tuberculosis (TB) between Vietnam and Japan. • To prevent generation and spread of drug-resistant TB. **Output** A. NCGM-RIT-HLH collaboration 1. Analysis of Hanoi-TB data containing clinical, genome-epidemiological, immunological and bacteriological	

	information, and specimens. 2. Improvement of diagnosis, monitoring, treatment and prevention of TB and understanding process of TB infection and development. 3. Identification and reduction of risk factors to prevent spread of drug-resistant TB. 4. Identification of possible risk factors to unfavorable anti-TB treatment outcomes. B. NCGM-RIT-NLH collaboration 1. Analysis of Hanoi-TB data containing clinical, genome-epidemiological, immunological and bacteriological information, and specimens. 2. Improvement of diagnosis, monitoring, treatment and prevention of TB and understanding process of TB infection and development. 3. Identification and reduction of risk factors to prevent spread of drug-resistant TB. 4. Identification of possible risk factors to unfavorable anti-TB treatment outcomes.

Research No.8

1	Title (in English)	Research on latent tuberculosis infection among healthcare workers in Hanoi, Vietnam
2	Title (in Japanese)	ベトナムにおける結核症に関する研究 潜在性結核感染のバイオマーカーに関する研究
3	Main researcher	Naoto Keicho (NCGM/Research Institute of Tuberculosis, JATA) Pham Huu Thuong (Hanoi Lung Hospital)
4	Co-Researcher(s)	Vu Cao Cuong (Hanoi Department of Health) Hoang Van Huan (Hanoi Lung Hospital) Do Bang Tam (Hanoi Lung Hospital) Minako Hijikata (NCGM/Research Institute of Tuberculosis, JATA) Nguyen Thi Le Hang (NCGM-BMH Medical Collaboration Center)
5	Resource of fund	The Research Program on Emerging and Re-emerging Infectious Diseases, AMED
6	Affiliation(s) in Viet Nam	Hanoi Lung Hospital (HLH), Vietnam
7	Period of the research	2018-2020
8	Publications	**A transcriptomics approach to biomarkers for latent tuberculosis infection using next generation sequencer** Minako Hijikata, Ikumi Matsushita, Shintaro Seto, Naoto Keicho (non-member: Nguyen Thi Le Hang, Do Bang Tam, Vu Cao Cuong, Pham Huu Thuong) Presented at the 93rd Annual Meeting The Japanese Society for Tuberculosis 2018/6/23-6/24 Osaka **A study on miRNA signature in the whole blood of individuals with latent tuberculosis infection** Minako Hijikata, Nguyen Thi Le Hang, Do Bang Tam, Ikumi Matsushita, Shintaro Seto, Vu Cao Cuong, Pham Huu Thuong, Naoto Keicho Presented at The American Society for Microbiology Conference on Rapid Applied Microbial Next-Generation Sequencing and Bioinformatic Pipelines 2018/9/23 -9/26.
9	Summary: **Overall purpose** • To strengthen collaborative research work on tuberculosis (TB) between Vietnam and Japan. • To study immunity of latent tuberculosis infection for a better prevention of tuberculosis. **Output** 1. To understand human immunity of latent tuberculosis infection, and the process of TB infection and development. 2. To identify risk factors of tuberculosis infection including occupational factors. 3. To identify possible biomarkers for tuberculosis infection.	

Research No.9

1	Title (in English)	Support for Strengthening Medical Treatment Ability of the Childhood Cancer in Viet Nam
2	Title (in Japanese)	ベトナムにおける小児がん医療の診療能力強化を目的とした支援
3	Main researcher	Hiroyuki Shichino (Director of pediatrics, NCGM)
4	Co-Researcher(s)	Noriko Sato, Junko Yamanaka, Hideko Uryu, Mizue Tanaka, Yuri Yoshimoto
5	Resource of fund	International Promotion of Japan's Healthcare Technologies and Services, NCGM Program International Health Research (A27-5) from Ministry of Health Labor and Welfare of Japan
6	Affiliation(s) in Viet Nam	National Hue Central Hospital (Hue) Ho Chi Minh Children Hospital 1 (HCM city) Ho Chi Minh Children Hospital 2 (HCM city) Ho Chi Minh Children Hospital 3 (HCM city) National Children Hospital (Hanoi) National Cancer Hospital (Hanoi)
7	Period of the research	April 2018 - March 2019
8	Publications	None
9	Summary:	

Background:

Eighty percent of childhood cancer patients are children in the developing countries. There are many problems such as misdiagnoses, delay of discoveries, lack of offer for treatment. Actually there was not the grasp of accurate number of the childhood cancer patients in those countries and many childhood cancer patients were supposed to be untreated.There were small numbers of specialists of pediatric cancer.

Purpose:

To support for strengthening diagnosis, medical treatment, supportive care abilities of the childhood cancer in the pediatrics, pediatric surgery, and radiological diagnosis and treatment of leading hospitals in Viet Nam.

Methods:

1. Sending experts who are well-versed in childhood cancer from Japan, to provide training in the field of childhood cancer diagnosis, treatment, supportive care.
2. Accepting healthcare providers from Viet Nam as trainees for studying childhood cancer.
3. Making a new style of consulting system through the internet cloud environment.

Result:

We sent total 10 Japanese experts to Hue central hospital, Ho Chi Minh Children Hospital 1. And accepted 6 doctors from Hue, Ho Chi Minh City and Hanoi into Japan. And started to use new consulting system in Hue and Ho Chi Minh. In Hue Central Hospital, there increased the number of children with solid tumors. They didn't treat any children at all in 2016 but they treated more than 50 children until 2018. From Ho Chi Minh Children Hospital 1 they sent more than 15 cases of consulting during 2016-2018.

Conclusion:

We could support to improve the medical treatment ability of the staff concerned with childhood cancer about such as a diagnosis, treatment, nursing care, supportive care. And also we thought we could increase the number of childhood cancer patients who had been diagnosed and treated step by step. Consulting system would be useful to keep in touch and continuing of study.

At Hue Central Hospital

At the Annual Meeting of Viet Nam Cancer Association

2. Other activities, topics

2.1 International Nursing Practicum for Nursing Students at the National College of Nursing, Japan

We conducted a one-week nursing practicum in Viet Nam as part of the elective subject of International Nursing Practicum for fourth-year undergraduate students in collaboration with Hai Duong Medical Technical University (HMTU), Viet Nam.

The International Nursing Practicum is designed to enhance student's' abilities to understand the current situation of nursing and health care practice in developing countries, whereby promoting the development of nursing theory with international perspectives to facilitate international health cooperation in nursing. As a prerequisite, students are required to complete the international nursing theory course.

Students were divided into groups, and each group was assigned several presentation topics to work toward the goals of the practicum. Before departing for Hai Duong, Viet Nam, where the practicum took place, students rehearsed their presentations in English in order to improve the quality of presentation and share their knowledge among groups in preparation for the practicum.

On the first day of the practicum, students gave their presentations in front of the faculty members and undergraduate students at HMTU and NCNJ. They then visited several institutions in Hanoi city and Hai Duong province, such as a provincial hospital, a district hospital, a specialty hospital, a leprosy village, a social welfare institution, and a community health center.

On the last day of the practicum, each group presented the summary of students' experiences at Bach Mai Hospital. Back in Japan at NCNJ, a poster presentation was held in the entrance hall, which gave students an opportunity to summarize what they had learned through the practicum in both Japan and Viet Nam, as well as to inform other junior students and faculty members of their valuable experiences.

Student evaluation revealed that most students wished to contribute what they had learned to nursing activities in Japan and promotion of international health cooperation.

2.2 International Clinical Trial Network Development

Tatsuo Iiyama
Sr. Manager, Department of International Trials,
Center for Clinical Sciences, NCGM

We established the "Department of International Trials" at the NCGM (DIT-NCGM) in 2016, aiming for international cooperation in R&D of medical products against neglected diseases.

Our activities include: developing a network with counterpart countries, sharing information of medical technologies, capacity-building, discussion for mutual R&D strategies, planning and implementing projects for new medical products.

For efficient cooperation with Asian countries, half of the DIT-NCGM staff are from counterpart countries, including Vietnam.

Followings are our activities in 2018 with Viet Nam;

Short term training program: Sakura Science Program (Youth exchange program)

The Sakura Science Program aimed at sharing the science, ethics and regulations of clinical trials with cutting-edge topics. For this purpose, the DIT-NCGM co-organized with the Disease Control and Prevention Center (DCC) a 10-day training program at the NCGM and collaborative institutions.

Participants, as future leaders of medical innovations, gathered from 4 Asian countries including Viet Nam, and had fundamental and advanced experiences in terms of R&D via clinical trials (See the attached the program).

Location: Tokyo

Period: 16th -24th Jan 2018

Contents: Clinical Trial Methodology, Topics of Cutting-edge Medical Innovation, Infections

Participants: 8 clinicians and researchers from 4 countries (IDN, PHL, THA, VNM)

URL: https://ssp.jst.go.jp/report2017/k_vol310.html

Announcement of current Vietnamese conditions at the "NCGM IID Forum"

The NCGM International Infectious Disease Forum (NCGM IID Forum) is a Public-Private Partnership platform of medical interventions with members from government agencies, academic institutions, industrial companies and funding agencies.

At the 2nd NCGM IID Forum held in Tokyo, the Vietnamese regional manager of DIT-NCGM presented

updates on current conditions of clinical systems, research activities and regulatory affairs in Viet Nam to over 100 participants.

Location: Tokyo

Period: 20th July 2018

Contents: “Overview of Global Clinical Research Network Bases Project”

Participants: Lecturers from IDN, PHL, THA, VNM, USA, and Japan. Audience of 136.

III. The program for international promotion of Japan's healthcare technologies and services 2018

This program has been commissioned by the Ministry of Health, Labour and Welfare Japan since fiscal 2016. The purpose is to extend Japanese healthcare and services as well as experiences on health systems to the world. Areas of the program include (1) Japanese health technologies, medical devices, and medicines, (2) management of health facilities, (3) health regulation, medical insurance, medical environment management, (4) health information systems, and (5) global health issues such as emerging and re-emerging infectious diseases, an aging society, maternal and child health, nutrition, non-infectious diseases, and disaster response. The program consists of two methods; dispatch of Japanese specialists and acceptance of foreign trainees in Japan.

Project Title: Project of developing Surgical Team Medicine/Care based on Bach Mai Hospital

Project to Support Improvement of the Quality of Stroke Care in the Socialist Republic of Viet Nam - Introduction of a Comprehensive Team Care for Stroke

Program manager: HARA Tetsuo Vice Director of Center Hospital

Objective: The objectives of Improvement of the Quality of Surgical Medical Treatment and Care by Comprehensive Team Approach to medical care by based on Bach Mai Hospital

Program outline:

Activity 1: Support Improvement of the Quality of Stroke Care - Introduction of a Comprehensive Team Care for Stroke in Vietnam

Activity 2: Support of Nosocominal Infection Control and Pain Control in Preoperative Medicine

Activity 3: Technical Support Improvement of the Medical Equipment

Implementation structure NCGM and BMH:

Activity 1: Neurosurgery/Nursing/Pharmacy/Nutrition/Rehabilitation

Activity 2: Anesthesiology and Operation department /ICU

Activity 3: Medical Equipment Department

[Report] Activity 1: Neurosurgery/Nursing/Pharmacy/Nutrition/Rehabilitation

To improve the quality of stroke care in Vietnam, we carried out the activities to support comprehensive team of medical care. Specific activities: (1) Dispatch of Expert from NCGM (2) Dispatch of Expert from BMH, (3) Web Meeting between NCGM and BMH.

The role of this project is comprehensive team focused on stroke care team and many kinds of work such as neurosurgical doctor, rehabilitation department doctor, SCU ward nurse, pharmacist, nutritionist, etc. are working in cooperation.

Schedule in 2018

1. 31 January 2018 - 3 February 2018 : Dispatch of Expert from NCGM
2. 6 June 2108 - 9 June 2018: Dispatch of Expert from NCGM
3. 6 September 2018: Web Meeting between NCGM and BMH
4. 14 October 2018 - 27 October 2018 : Dispatch of Expert from BMH

- **Neurosurgery**

Database of Neurosurgery were examined because there was a desire to create a database of cases in which cranial neurosurgery, especially cranial aneurysm, was performed with craniotomy and cranial arteriovenous malformations performed craniotomy. In addition to the age, gender, severity, surgical contents, presence / absence of complications, etc., the items described include a wide range of subjects, including the date of onset of postoperative rehabilitation, the occurrence of aspiration pneumonia; It was reflected the results of activities of the project. We have made a prototype of the database and were currently revising it to make it more practical at BMH. BMH staffs visited to the clinical site in Japan at the training in Japan and conducted training on specific medical care for stroke care.

- **Rehabilitation**

In order to establish a comprehensive team medicine through multi-occupational collaboration and aim to improve the level of stroke care in Vietnam, we worked on establishing the acute rehabilitation of stroke in the neurosurgery ward at Bach Mai hospital. Specific contents include: ①Enhancement of acute period bedside rehabilitation in neurosurgery ward ②Introduction of swallowing screening test in neurosurgery ward ③Introduction of swallowing food in Vietnam for the first time ④Assistance in manual preparation of hospital rehabilitation ⑤Technology transfer by ST for individual instruction ⑥Multiple occupation Conference ⑦We made effective use of the materials provided.

In addition, as contents of training in Japan, ①Visit to the department related to stroke diagnosis ②Stroke acute phase rehabilitation (early exit from bed, respiration rehabilitation, swallowing assessment) ③Practical training for training records and data compilation ④Multi-occupational collaboration (nursing, nutrition, medical Department of Joint Program) ⑤Multi-occupation conference visit ⑥Risk management of acute rehabilitation ⑦Preparation of family guidance materials ⑧Other facilities tour ⑨Group work .

Through the activities of this fiscal year, in order to enhance acute rehabilitation of stroke in the neurosurgery ward, we felt a growing awareness that team medicine through multi-occupational collaboration is important and the momentum to promote them. In addition, we were able to visit a

fulfilling to visit to Bach Mai Hospital and training at NCGM, and we were achieved on outcome indicators and training object in the training at NCGM with consultation and agreement between BMH and NCGM

I would like to continue the activities to promote the acute rehabilitation of stroke care by multi-occupational collaboration by making opportunities for multi-occupational activities to work together.

- **Nursing**

In order to promote nursing practical skills and understanding of the role of nursing in medical team, we have supported activities of lectures and exercises for strengthening nursing practical skills (leaving bed, swallowing function observation and assessment) and other occupational collaboration for medical care.

In the follow-up visit, we confirmed on the situation of nursing practice with the two counterparts at the neurosurgical ward of Bach Mai Hospital, and exchange the opinions about team medical care, autonomy, expertise of nursing with the cranial nerve surgery ward and the management for improvement.

From the beginning of this project, it was possible to acquire cooperation between the neurosurgical ward nurse and the therapist about the swallowing and leaving bed, which is the theme for realizing medical team, and although it is a very small case, intervention for function improvement. Under the guidance of a therapist, we also started patient and family guidance by making use of pamphlets (made by therapists). Although it is a limited period of 25th June 2018 to 25th September 2018 (about 3 months), We were preparing a report that summarizes the results of the intervention . However, monitoring is a role of nursing and a risk assessment for avoiding complications is necessary, and knowledge and technology for that need to be improved. In the current medical provision system in Vietnam, there is no doubt that the key person in patient recovery and life is family, but because of the lack of the absolute number of care providers such as nurses and therapists, There is a present condition that care is concentrating on families.

We think it is a matter of nursing to care for families who are consumers, and it is a task of realizing medical team care in Vietnam.

- **Pharmacy**

Based on last year's training, a pharmacist also participated in the round of the neurosurgical ward in January and started accompanying a round. As a result, prescription proposal by pharmacist could be implemented from the viewpoint of proper use of medicine. The number of case interventions received 7 reports in January, 3 in February, 3 in March, 2 in April, and 5 in May. This is the first activity that a clinical pharmacist goes to a patient bedside and discusses medication with a doctor.

We participated in "The First Bach Mai hospital clinical pharmacy conference" for clinical pharmacists

in northern Vietnam held in BMH in April and gave a lecture entitled "Clinical pharmacy services in Japan". We introduced the work of clinical pharmacists in Japan and exchanged views with clinical pharmacists in Vietnam.

When we visited BMH in June, we got information that there are scattered examples of crushing drugs that are not pulverized in the neurosurgical ward. As a countermeasure, we suggested the creation of a list of incompatible drugs, and based on that proposal, the BMH pharmacist created a list of incompatible drugs. In addition, we gave a lecture on the simple suspension method as a new medicine administration method from intubation in the Japanese training in October, and provided information on administration of medicines in a safe and simple way. After training, we are informed by implementing a lecture aimed at sharing information to other occupational types based on the list of incompatible drugs by BMH pharmacists.

- **Nutrition**

There was not swallowing food for eating dysphagia after stroke surgery in July 2017, when we visited to Bach Mai Hospital (BMH) on Vietnam. After that, we negotiated with the nutrition center in BMH, and aimed to introduce swallowing meal to BMH. As a result, ①it was introduced three kinds of swallowing foods of levels 1 to 3 at the time of the follow-up visit in January 2018. ②Swallowing food was offered to 10 patients. ③ST proposed swallowing assessment, the appropriate level to the doctor, cooperation with multi-occupation where the doctor provides after the order is provided by the nutritionist was established. ④The number of nutritional diet guidance to patients with swallowing disorder increased from 0 to 5 cases. ⑤Dietitians began participating in the neurosurgical conference was involved.

Based on the above results, as a model of neurosurgery in the fiscal year 2018, ①To introduce swallowing food into the whole department and record the number of offerings. ②To conduct sharing meeting on swallowing food for staff of other departments in BMH and hospitals. ③To introduce a jelly-started meal was set as a next subject.

In addition, we discussed with the aim of holding a seminar on swallowing food in January2019, cooperated with BMH, NCGM, 3 Japanese companies (Ajinomoto Foundation, Neutri Co., Ltd., Mitsubishi Corporation FoodTech).

The number of swallowing meals has increased with demand; 1609 meals of swallowing food in December of 2018. It was offered swallowing food more than 9000 from November 2017 until December 2018. The problem is that it is not possible to purchase thickening food that are used stably for swallowing food, despite the increasing demand for swallowing foods.

(1) Teaching guidance on swallowing screening examinations at Bach Mai hospital Neurosurgery ward

(2) Introduction of Vietnam's first swallowing food

(3) Practice at SCU/NCGM

(4) A situation of multi-occupational group work in training in Japan

[Report] Activity 2: Anesthesiology and Operation department /ICU

We carried out the activities to support comprehensive team of medical care. Specific activities: (1) Dispatch of Expert from NCGM (2) Dispatch of Expert from BMH, (3) Web Meeting between NCGM and BMH.

The role of this project is comprehensive team focused on Management of Ventilator Associated Pneumonia and Pain Control in Preoperative Medicine.

Schedule in 2018

1. 15 January 2018 - 18 January 2018 : Dispatch of Expert from NCGM
2. 11 June 2108 - 15 June 2018: Dispatch of Expert from NCGM
3. 6 September 2018: Web Meeting between NCGM and BMH
4. 8 October 2018 - 17 October 2018 : Dispatch of Expert of BMH for training in NCGM

Training contents (what trainees will study) in Preoperative Care

- Effective infection control and pain management in Perioperative care are achieved

For Doctor

- WHO surgical safety checklist is regularly used and recorded Practice and Lecture on side
- Management of Ventilator Associated Pneumonia : Practice and Lecture on side
- Management of Pain Control

For Nurse

- Shadowing the patient flow and clarify the difference between Vietnam and Japan in operation
- Follow whole process in cleaning, sterilization & maintenance of surgical instruments in NCGM
- Lecture on cleaning, sterilization & maintenance of surgical instruments by specialist

(1) Lecture at ICU/NCGM

(2) Observation at Operation room/ Kounodai Hp NCGM

[Report] Activity 3: Medical Equipment Department

We carried out the activities to support comprehensive team of medical care. Specific activities: (1) Dispatch of Expert from NCGM (2) Dispatch of Expert from BMH, (3) Web Meeting between NCGM and BMH.

The role of this project is comprehensive team focused on improvement of the medical equipment management.

Schedule in 2018

1. 18 June 2108 - 23 June 2018: Dispatch of Expert from NCGM
2. 6 September 2018: Web Meeting between NCGM and BMH
3. 10 September 2018 - 14 September 2018 : Dispatch of Expert of BMH for training in NCGM
4. 5 December 2018 -12 December 2018 : Dispatch of Expert from NCGM

Outcome

Medical Engineers(MEs) conduct QA/QC (Quality Assessment and Quality control)

Training contents

- Observation NCGM: ICU other department related with ME Dep.
- Situation of management of Medical device in Japan
- Outsorcing about medical device management
- System of Clinical Engineering
- Visit to Medical Device Company in Japan
- Visit Private University Hospital (Teikyo university hospital)

(1) Demonstration on ME seminar in BMH

(2) Practice at ME dep./NCGM

IV. Reference

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Original Article

Tenofovir disoproxil fumarate co-administered with lopinavir/ritonavir is strongly associated with tubular damage and chronic kidney disease

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Lopinavir boosted with ritonavir

ABSTRACT

Backgroud: With expanding antiretroviral therapy (ART) in a resource-limited setting, the use of second line ART with ritonavir boosted lopinavir (LPV/r) is increasing. However, little is known regarding the renal safety of tenofovir (TDF) co-administered with LPV/r.

Methods: In total 1382 HIV-infected patients were enrolled and data were recorded twice (October 2014 and 2015) in Vietnam. Tubular dysfunction (TD) was defined as urinary beta 2 microglobulin (β2MG) > 1000 μg/L at both timepoints or increase in β2MG by > 2000 μg/L. Chronic kidney disease (CKD) was defined as creatinine clearance ≤60 ml/min or urinary protein/creatinine ratio ≥ 0.15 g/gCre at both timepoints.

Results: The patients'mean weight and age were 55.9 kg and 38.4 years, respectively, and 41.5% were female. Additionally, 98.2% were on ART, 76.3% were on TDF (mean exposure duration was 35.4 months), and 22.4% had never TDF exposure. TD and CKD were diagnosed in 13% and 8.3% of all patients, respectively. In multivariate analyses, age (OR = 1.057; 95%CI, 1.034–1.081), being female (OR = 0.377; 95%CI, 0.221–0.645), HBsAg positive (OR = 1.812; 95%CI, 1.134–2.894), HCVAb positive (OR = 1.703; 95% CI, 1.100–2.635), TDF exposure (OR = 9.226; 95%CI, 2.847–29.901) and LPV/r exposure (OR = 5.548; 95% CI, 3.313–9.293) were significantly associated with TD. Moreover, age (OR = 1.093; 95%CI, 1.068–1.119), being female (OR = 0.510; 95%CI, 0.295–0.880), weight (OR = 0.909; 95%CI, 0.879–0.939), hypertension (OR = 3.027; 95%CI, 1.714–5.347), TDF exposure (OR = 1.963; 95%CI, 1.027–3.7 53) and LPV/r exposure (OR = 3.122; 95%CI, 1.710–5.699) were significantly associated with CKD.

Conclusions: TDF and LPV/r exposure were strongly associated with TD and CKD, in addition to their known risks. Therefore, attention to renal safety for patients on second line ART is necessary.

1. Introduction

Renal dysfunction is fast becoming one of the major comorbidities among HIV-infected patients since widespread use of antiretroviral therapy (ART) has decreased AIDS-associated mortality [1,2]. Antiretroviral drugs (ARVs) can cause renal dysfunction in addition to HIV infection itself. Among various ARVs which affect renal function [3–5], tenofovir disoproxil fumarate (TDF) is the only ARV that WHO guidelines recommend as the first line nucleotide reverse transcriptase inhibitor (NRTI) in combination with lamivudine (3 TC) or emtricitabine (FTC) [6]. Thus, TDF is being commonly used as the first choice in many countries. Furthermore, in resource limited settings TDF is frequently co-administered with the protease inhibitor ritonavir-boosted lopinavir (LPV/r), which is also a known risk factor for

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renal dysfunction, as a salvage regimen recommended by WHO guidelines [4]. Although clinical trials and a meta-analysis reported that TDF-associated nephrotoxicity is only modest [7], several studies suggest that TDF causes renal proximal tubular dysfunction and renal dysfunction in a clinical setting, such as when TDF is co-administered with LPVr [8,9]. In many resource limited settings, the frequency of co-administration of TDF and LPV/r and the period of exposure has been increasing. The long term renal safety of TDF and LPV/r is of concern in this context.

The mechanism of TDF-induced renal dysfunction is not fully understood. One hypothesis is that accumulated TDF in renal proximal tubule cells causes mitochondrial toxicity, which is a well-known adverse effect of NRTIs, and leads to tubular dysfunction [10]. Subsequently, the renal tubular dysfunction could develop into renal dysfunction which presents as a decrease in estimated glomerular filtration rate or increase in urinary protein. Thus, to detect tubular dysfunction caused by TDF before renal dysfunction develops is clinically important. Several studies reported that urinary beta 2 microglobulin (β2MG) is a useful marker for TDF-associated tubulopathy in HIV-infected patients [11–15]. In contrast, regarding the mechanism of LPV/r-associated nephrotoxicity, although the influence of LPV/r on renal function remains controversial, it is thought to be due to increased TDF concentration in renal proximal tubular cells rather than a direct effect of LPV/r itself on renal function [16,17].

Furthermore, low body weight was reported to be a risk factor for tubular and renal dysfunction caused by TDF in Japanese studies with an average body weight of approximately 65 kg [18,19]. In Japan, tenofovir alafenamide (TAF), which possesses a safer renal function profile compared with TDF, is therefore being substituted for TDF. However, due to budgetary constraints, TDF is still the predominantly used ARV in the majority of the world, including Asian countries, where body weight is smaller still than that of the Japanese. We previously reported that low body weight and use of TDF are risk factors for renal dysfunction in Vietnamese HIV-infected patients, where the average body weight was approximately 55 kg [20,21]. In these populations with smaller body weight, evidence on tubular and renal dysfunction caused by TDF is limited.

Therefore, we conducted a cross-sectional study to evaluate the prevalence of tubular and renal dysfunction and their associated factors, and to estimate the association between tubular and renal dysfunction and exposure of TDF and LPV/r in Vietnamese HIV-infected patients.

2. Patients and methods

2.1. Study design

We conducted a cross-sectional study in an observational single-center cohort of Vietnamese HIV-infected patients. This study was performed at the National Hospital for Tropical Disease (NHTD), Hanoi, Vietnam, one of the largest out-patient clinics for HIV infected-patients in Vietnam. The study population included Vietnamese HIV-infected patients aged more than 17 years, who presented at NHTD from October 2014 to October 2015. The study was approved by the Human Research Ethics Committee of the National Hospital for Tropical Disease and Hanoi city, Hanoi. All patients recruited in the study provided written informed consent for their clinical and laboratory data to be used and published for study purposes. The study has been performed according to the principles expressed in the Declaration of Helsinki.

2.2. Measurements

Data collection was performed twice, in October 2014 and October 2015, for every patient registered in the cohort. Data included demographic variables (height, weight, sex and age); systolic and diastolic blood pressure (mmHg); a complete history of ART; use of drugs for prophylaxis against opportunistic infections; fasting blood sugar (mg/dL); CD4 cell counts (cells/mm^3, measured by flow cytometry); plasma HIV-RNA (copies/ml, measured by the Roche Cobas Taqman analyzer; Roche Molecular Diagnostics, Pleasanton, CA); Hepatitis B virus surface antigen and hepatitis C virus antibody were both measured by ECLIA method; serum creatinine (sCre) (mg/dl, measured by the Jaffe method); urinary beta 2 microglobulin (β2MG) (μg/L; DENKA SEIKEN Co. Ltd., Tokyo, Japan); urinary protein (g/L) and urinary creatinine (g/L). Hypertension was defined as systolic pressure greater than 140 mmHg or diastolic pressure greater than 90 at both timepoints. Diabetes mellitus was defined as fasting blood glucose concentration greater than 126 mg/dL at both timepoints. Tubular dysfunction was defined as β2MG levels greater than 1000 μg/L at both timepoints or an increase in β2MG of more than 2000 μg/L. CKD was defined as Ccr less than 60 ml/min at both timepoints or urinary protein/creatinine ratio (uP/C) more than 0.150 g/gCre at both timepoints. Ccr was assessed using the Cockcroft-Gault equation.

2.3. Statistical analysis

Statistical analysis included descriptive (mean and standard deviation), univariate and multivariate analyses. Absolute and relative frequencies were used for continuous and categorical variables, respectively. To evaluate the association between TD, CKD and categorical variables, Chi-square or Fisher's exact tests were applied as required. Independent t tests or one way ANOVA were used to compare means and, in case of asymmetry, Mann Whitney or Kruskal-Wallis tests were also used. Variables significantly associated with TD and CKD in univariate analysis were included in the multivariate analysis. Poisson Regression was used to determine the factors associated with TD and CKD in univariate analysis and multivariate analysis. Statistical significance was defined as a two-sided p value < 0.05. We used odds ratios (OR) and 95% confidence intervals (95% CIs) to estimate the association of each variable with TD and CKD. All statistical analyses were performed with SPSS ver. 22.0 (IBM SPSS, Chicago, IL).

3. Results

Table 1 shows the baseline characteristics of the study participants. 1382 Vietnamese HIV-infected patients fulfilled the study criteria. They were on average 38.4 years old and 41.5% of the patients were female. The average body weight and body mass index were 55.9 kg and 21.3 kg/m^2, respectively, which represents a population with considerably low body weight. The prevalence of hypertension and diabetes mellitus were 9.4% and 1.6%, respectively. Of the total patients, 1357 patients were on ART and 1036 patients (76.3%) were taking TDF, 17 patients (1.3%) had been taking TDF and then discontinued previously, and 304 patients (22.4%) had never been exposed to TDF. Apart from TDF, zidovudine (AZT) or stavudine (d4T) were mainly used in combination with 3 TC. The average duration of TDF administration was 35.4 months, which is relatively short compared with that of ARV administration, which was 63.3 months. 10% of the patients on ART were taking LPVr and the rest of the patients were taking NNRTIs, either efavirenz (EFV) or nevirapine (NVP). More than 95% of the patients on ART achieved viral suppression.

Table 1
Baseline characteristics of Vietnamese patients according to history of TDF use.

Variables	Overall (n = 1382)	Current TDF (n = 1036)	Previous TDF (n = 17)	No TDF exposure (n = 304)	Naïve (n = 25)
Age, years	38.4 ± 8.6	38.6 ± 8.4	42.1 ± 7.1	37.9 ± 9.2	34.2 ± 6.0
Female, n (%)	573 (41.5)	356 (34.4)	8 (47.1)	189 (62.2)	20 (80.0)
Body weight, kg	55.9 ± 8.6	56.5 ± 8.6	54.2 ± 7.2	53.8 ± 8.2	54.9 ± 8.6
HBsAg (+), n (%)[a]	168 (16.5)	162 (15.6)	1 (5.9)	4 (1.4)	1 (6.7)
HCVAb (+), n (%)[a]	468 (39.1)	407 (45.2)	2 (11.8)	56 (21.1)	3 (20.0)
Systolic blood pressure, mmHg[a]	118.8 ± 15.6	118.9 ± 15.8	125.6 ± 14.0	118.2 ± 15.2	115.05 ± 10.2
Diastolic blood pressure, mmHg[a]	78.3 ± 12.5	78.8 ± 12.5	81.1 ± 10.7	76.8 ± 12.4	77.0 ± 9.6
Hypertension[a]	128 (9.4)	94 (9.3)	2 (11.8)	31 (10.2)	1 (4.3)
Fasting blood sugar, mg/dL[a]	91.4 ± 21.0	92.0 ± 21.7	86.9 ± 12.0	84.5 ± 19.0	N.A.
Diabetes mellitus (+), n (%)[a]	21 (1.6)	16 (1.6)	0 (0)	5 (1.7)	N.A.
$CD4^+$ cell count, cell/μl	462.6 ± 207.2	448.2 ± 196.9	459.4 ± 247.2	505.9 ± 236.2	532.5 ± 122.4
HIV RNA <50 copies/ml, N (%)	1304 (94.4)	990 (95.6)	17 (100)	296 (97.4)	1 (4.0)
Time since HIV diagnosis, months	79.5 ± 47.6	77.8 ± 48.5	94.1 ± 58.2	86.5 ± 43.3	52.9 ± 36.5
Time since initiation of ART, month	63.3 ± 37.3	61.6 ± 38.3	72.2 ± 47.9	68.4 ± 32.4	
Time on TDF, months	35.4 ± 18.6	35.7 ± 18.4	21.4 ± 24.9		
Time since cessation of TDF	29.8 ± 22.9		29.8 ± 22.9		
Currently on LPV/r	138 (10.0)	122 (11.8)	8 (47.1)	8 (2.6)	
Time on LPV/r	54.7 ± 27.4	55.0 ± 27.1	38.4 ± 31.1	69.0 ± 19.3	
Previous exposure to LPV/r	7 (0.5)	6 (0.6)	1 (5.9)	0 (0)	
Time since cessation of LPV/r	25.9 ± 7.8	26.8 ± 8.1	20		
Current use of co-trimoxazole, n (%)	90 (6.5)	78 (7.5)	0 (0)	12 (3.9)	0 (0)

Data are expressed as the mean ± SD or n (%). HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibody; ART = antiretroviral therapy; TDF = tenofovir disoproxil fumarate; LPV/r = ritonavir boosted lopinavir.
[a] There are missing data.

Regarding TD and renal dysfunction, Table 2 demonstrates that the level of urinary β2MG, the prevalence of TD and the prevalence of CKD were significantly higher among patients who were taking or had been exposed to TDF than among patients who had not been exposed to TDF. In particular, although a small number of the cases, it is noteworthy that TD and CKD still remained even after withdrawal of TDF for an average of 30 months.

In Table 3, factors associated with TD among the patients on ART were evaluated in uni- and multivariate analyses. By multivariate analysis, age (OR = 1.057; 95% CI, 1.034–1.081; $p < 0.001$), female sex (OR = 0.377; 95% CI, 0.221–0.645; $p < 0.001$), HBsAg positive (OR = 1.812; 95% CI, 1.134–2.894; $p = 0.013$), HCVAb positive (OR = 1.703; 95% CI, 1.100–2.635; p = 0.017), exposure to TDF (OR = 9.226; 95% CI, 2.847–29.901; $p < 0.001$) and exposure of LPV/r (OR = 5.548; 95% CI, 3.313–9.293; $p < 0.001$) were significantly associated with TD. Table 4 identified factors associated with CKD among the patients on ART in uni- and multivariate analyses. In multivariate analysis, age (OR = 1.093; 95% CI, 1.068–1.119; $p < 0.001$), female sex (OR = 0.510; 95% CI, 0.295–0.880; $p = 0.016$), body weight (OR = 0.909; 95% CI, 0.879–0.939; $p < 0.001$), hypertension (OR = 3.027; 95% CI, 1.714–5.347; $p < 0.001$), exposure to TDF (OR = 1.963; 95% CI, 1.027–3.753; $p = 0.041$) and exposure to LPV/r (OR = 3.122; 95% CI, 1.710–5.699; $p < 0.001$) were significantly associated with CKD. Interestingly, not only TDF but also LPV/r was strongly associated with TD and, regarding CKD, LPV/r seems to be an even stronger factor than TDF in this population. This finding is important, given that the current WHO guideline recommends use of LPV/r as a salvage regimen and it is often used in conjunction with TDF. Furthermore, in uni- and multivariate analyses among the patients who were taking or exposed to TDF previously, factors significantly associated with TD were age (OR = 1.054; 95% CI, 1.030–1.079; $p < 0.001$), female sex (OR = 0.169; 95% CI, 0.091–0.314; $p < 0.001$), body weight (OR = 0.923; 95% CI, 0.898–0.950; $p < 0.001$), duration of TDF administration (OR = 1.014; 95% CI, 1.002–1.026; $p = 0.020$) and exposure to LPV/r (OR = 4.535; 95% CI, 2.677–7.685; $p < 0.001$) (table not shown). Factors significantly associated with CKD in this population were age (OR = 1.093; 95% CI, 1.065–1.122; $p < 0.001$), female sex (OR = 0.367; 95% CI, 0.196–0.689; $p = 0.002$), bodyweight (OR = 0.893; 95% CI, 0.859–0.927; $p < 0.001$), hypertension (OR = 2.909; 95% CI, 1.535–5.512; $p = 0.001$), duration of TDF administration (OR = 1.022; 95% CI, 1.007–1.037; $p = 0.005$) and exposure to LPV/r (OR = 3.046; 95% CI, 1.599–5.801; $p = 0.001$).

To verify the hypothesis that TDF affects tubular function first which then develops into renal dysfunction, we evaluated the level

Table 2
Prevalence of renal proximal tubular dysfunction and renal dysfunction.

Variables	Overall (n = 1382)	Current TDF (n = 1036)	Previous TDF (n = 17)	No TDF exposure (n = 304)	Naïve (n = 25)
β2 microglobulin, μg/L	1142.8 ± 2838.2	1412.4 ± 3129.7	1918.4 ± 4386.6	250.6 ± 1028.9	294.9 ± 717.2
<500 μg/L, n (%)	1015 (73.4)	689 (66.5)	13 (76.5)	289 (95.1)	24 (96.0)
500 to 1000 μg/L, n (%)	129 (9.3)	121 (11.7)	0	8 (2.6)	0
1000 to 5000 μg/L, n (%)	151 (10.9)	143 (13.8)	2 (11.8)	5 (1.6)	1 (4.0)
>5000 μg/L, n (%)	87 (6.3)	83 (8.0)	2 (11.8)	2 (0.7)	0
Tubular dysfunction, n (%)	179 (13.0)	171 (16.5)	3 (17.6)	4 (1.3)	1 (4.0)
Urinary protein/creatinine ratio, g/gCre	0.088 ± 0.15	0.094 ± 0.16	0.119 ± 0.20	0.070 ± 0.13	0.069 ± 0.89
Proteinuria (>0.15 g/gCre) at both measurements, n (%)	74 (5.4)	63 (6.1)	2 (11.8)	8 (2.6)	1 (4.0)
Serum creatinine, mg/dl[a]	0.82 ± 0.19	0.84 ± 0.19	0.94 ± 0.31	0.75 ± 0.16	NA
Creatinine clearance, ml/min[a]	93.0 ± 20.8	92.7 ± 20.9	79.5 ± 25.6	94.5 ± 20.0	NA
Creatinine clearance < 60 ml/min at both measurements, n (%)	61 (4.5)	49 (4.7)	4 (23.5)	8 (2.6)	NA
Chronic kidney disease, n (%)	113 (8.3)	94 (9.1)	4 (23.5)	14 (4.6)	NA

Data are expressed as the mean ± SD or n (%). TDF = tenofovir disoproxil fumarate.
[a] There are missing data. The data of β2 microglobulin and urinary protein/creatinine ratio are expressed as of one point data at October 2015.

Table 3
Factors associated with tubular dysfunction estimated by uni- and multivariate analyses among HIV-infected patients on ART.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age	1.050	1.033–1.068	<0.001	1.057	1.034–1.081	<0.001
Female sex	0.212	0.137–0.326	<0.001	0.377	0.221–0.645	<0.001
Body weight	0.992	0.974–1.010	0.388			
HBsAg (+)	1.941	1.289–2.924	0.001	1.812	1.134–2.894	0.013
HCVAb (+) [a]	2.263	1.610–3.180	<0.001	1.703	1.100–2.635	0.017
Hypertension [a]	1.352	0.822–2.224	0.235			
Diabetes mellitus[a]	2.699	1.033–7.052	0.043	1.220	0.366–4.063	0.746
Current $CD4^+$ cell count, cell/μl	0.999	0.998–1.000	0.030	1.000	0.999–1.001	0.910
HIV RNA < 50 copies/ml	1.159	0.538–2.498	0.706			
Time since HIV diagnosis, months	1.004	1.001–1.007	0.013	1.000	0.993–1.007	0.936
Time since initiation of ART, months	1.007	1.003–1.012	<0.001	0.998	0.989–1.007	0.667
Exposure to TDF	14.846	5.463–40.349	<0.001	9.226	2.847–29.901	<0.001
Exposure to LPV/r	5.145	3.505–7.554	<0.001	5.548	3.313–9.293	<0.001
Use of co-trimoxazole	2.304	1.385–3.834	0.001	1.542	0.823–2.887	0.176

OR = odds ratio; CI = confidence interval; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibody; ART = antiretroviral therapy; TDF = tenofovir disoproxil fumarate; LPV/r = ritonavir boosted lopinavir.
[a] There are missing values.

of β2MG and other variables according to the status of TD and CKD among the patients who were taking or exposed to TDF. As shown in Table 5, the average level of β2MG increased with renal dysfunction, being 351.6, 4852.7 and 9869.3 μg/L in TD−/CKD-, TD+/CKD- and TD+/CKD + patients respectively. This also indicates that approximately 5000 μg/L urinary β2MG is a good reference value to predict possible CKD caused by TDF. The duration of TDF administration also increased, from 34.0, to 38.9, to 48.4 months these patient groups. In contrast, the duration of TDF administration was only 35.0 months in the TD-/CKD + patients, which is similar to the TD-/CKD-patients. The percentage of exposure to LPV/r was also considerably lower in the TD-/CKD + patients, which could reflect that LPV/r enhances the impact of TDF on tubular function. Regarding other comorbidities, the percentage of hypertension was substantially higher in the TD-/CKD + patients compared with the other groups. This could support speculation that CKD without TD is mostly not induced by TDF but by other known risk factors for CKD.

4. Discussion

We evaluated the prevalence of TD and CKD and its associated factors among well-controlled Vietnamese HIV-infected patients on ART with very low body weight in a clinical setting. The prevalence of TD and CKD in the patients who were taking TDF was 16.5% and 9.1%, respectively, which were 16.5 times and two times higher than those in patients without TDF exposure. The important finding is that not only the exposure to TDF but also to LPV/r was strongly associated with TD and CKD, in addition to other known risk factors. According to previous literature, renal toxicity caused by LPV/r is thought to be mostly due to enhanced impact of TDF on renal function when LPV/r is co-administered with TDF. LPV/r inhibits multidrug resistance proteins (MRP) transporter that actively efflux substances from proximal tubular cells into the proximal tubule lumen, which increases the concentration of TDF in proximal tubular cells and induces mitochondrial toxicity [16,17]. Previously, our group reported that low body weight and use of TDF are risk factors for renal dysfunction, since low body weight could lead to an over-dosage with a fixed dose of TDF [18–21]. The current data also suggested that low body weight is a risk factor for TD and CKD among the patients who were taking or exposed to TDF. Whether low body weight can also enhance the adverse effect of LPV/r should be evaluated in detail, taking into account that our current study indicated the impact of LPV/r on renal function was marked in this population with considerably smaller body weight compared with previous studies [4,22,23].

Table 4
Factors associated with chronic kidney disease estimated by uni- and multivariate analyses among HIV-infected patients on ART.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age	1.092	1.071–1.114	<0.001	1.093	1.068–1.119	<0.001
Female sex	0.585	0.384–0.892	0.013	0.510	0.295–0.880	0.016
Body weight	0.964	0.941–0.988	0.003	0.909	0.879–0.939	<0.001
HBsAg (+)	0.952	0.536–1.728	0.897			
HCVAb (+) [a]	1.119	0.745–1.680	0.588			
Hypertension [a]	4.334	2.714–6.921	<0.001	3.027	1.714–5.347	<0.001
Diabetes mellitus[a]	5.810	2.295–14.708	<0.001	1.158	0.356–3.771	0.807
Current $CD4^+$ cell count, cell/μl	0.998	0.997–1.000	0.005	0.999	0.998–1.000	0.184
HIV RNA < 50 copies/ml	0.443	0.104–1.804	0.250			
Time since HIV diagnosis, months	1.002	0.998–1.006	0.358			
Time since initiation of ART, months	1.007	1.002–1.012	0.004	1.003	0.996–1.009	0.401
Exposure to TDF	2.115	1.190–3.760	0.011	1.963	1.027–3.753	0.041
Exposure to LPV/r	2.995	1.867–4.803	<0.001	3.122	1.710–5.699	<0.001
Use of co-trimoxazole	2.628	1.473–4.690	0.001	1.996	0.970–4.107	0.060

OR = odds ratio; CI = confidence interval; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibody; ART = antiretroviral therapy; TDF = tenofovir disoproxil fumarate; LPV/r = ritonavir boosted lopinavir.
[a] There are missing values.

Table 5
Levels of β2 microglobulin and other variables according to presence of TD and CKD among the patients with exposure to TDF.

Variables	TD-/CKD- (n = 846)	TD+/CKD- (n = 107)	TD+/CKD+ (n = 67)	TD-/CKD+ (n = 31)
β2 microglobulin, μg/L	351.6 ± 375.5	4852.7 ± 3622.3	9869.3 ± 5359.6	569.1 ± 533.9
Age, years	37.7 ± 7.7	39.3 ± 7.9	45.9 ± 11.3	45.2 ± 12.2
Female, n (%)	326 (38.5)	13 (12.1)	13 (19.4)	11 (35.5)
Body weight	56.8 ± 8.8	56.7 ± 7.5	52.9 ± 6.6	55.3 ± 9.7
Current $CD4^+$ cell count, cell/μl	454.6 ± 193.3	451.1 ± 230.0	395.8 ± 213.4	382.9 ± 139.8
HIV RNA < 50 copies/ml, n (%)	809 (95.6)	101 (94.4)	65 (97.0)	31 (100)
HBsAg (+), n (%)[a]	126 (15.8)	23 (21.9)	13 (19.7)	1 (3.2)
HCVAb (+), n (%)[a]	312 (42.6)	57 (62.0)	29 (36.7)	11 (46.8)
Hypertension, n (%)	62 (7.3)	10 (9.3)	11 (16.4)	13 (41.9)
Diabetes mellitus, n (%)	10 (1.2)	0 (0)	6 (9.0)	0 (0)
Time since HIV diagnosis, months	76.0 ± 47.8	89.1 ± 52.9	87.2 ± 52.8	73.9 ± 43.2
Time since initiation of ART, month	59.3 ± 38.0	70.9 ± 36.8	77.0 ± 44.1	63.9 ± 33.6
Time on TDF, months	34.0 ± 17.8	38.9 ± 16.6	48.4 ± 23.8	35.0 ± 22.0
Exposure to LPV/r, n (%)	80 (9.5)	31 (29.0)	23 (34.3)	4 (12.9)
Use of co-trimoxazole, n (%)	53 (6.3)	9 (8.4)	13 (19.4)	3 (9.7)

OR = odds ratio; CI = confidence interval; TD = tubular dysfunction; CKD = chronic kidney disease; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibody; ART = antiretroviral therapy; TDF = tenofovir disoproxil fumarate; LPV/r = ritonavir boosted lopinavir.
[a] There are missing values.

Whether LPV/r itself directly affects renal function, like ATV and IDV which cause crystalluria, is controversial [24,25]. However, in sub-analysis of the patients who have not been exposed to TDF, LPV/r was not associated with TD (OR = 0.000; 95% CI, 0.000–; $p = 0.999$) nor CKD (OR = 0.000; 95% CI, 0.000–; $p = 0.999$) in univariate analysis, which suggests that the co-administration of TDF and LPV/r could be harmful in this population. Regarding the current WHO guidelines that recommend the combination of LPV/r and TDF/FTC as the second line regimen, substitution of other protease inhibitors such as ritonavir-boosted darunavir (DRV/r) or integrase inhibitors for LPV/r can be used as salvage regimens, especially considering that Jose et al. suggested that DRV/r may have a favorable renal safety profile compared with LPV/r [26].

Furthermore, another notable finding is that 5 patients showed no improvement in tubular or renal function even after TDF withdrawal. Several case reports illustrated that TDF-associated nephrotoxicity is reversible after withdrawal of TDF [27–29]. However, both Wever et al. and Jose et al. reported that normalization of renal function after withdrawal of TDF was incomplete in some cases [30,31], which is quite similar to our findings. Thus, early markers for renal dysfunction are important to detect renal damage before it becomes irreversible. In this sense, urinary β2MG might be a useful marker to detect TD and anticipate timing of a switch from TDF, assuming the hypothesis that TDF first causes tubular dysfunction which then deteriorates to renal dysfunction. According to the results, approximately 5000 μg/L of urinary β2MG and around 40 months of TDF administration might be indicators of possible renal dysfunction, especially if they are combined with other risk factors. Furthermore, the possibility of using urinary β2MG to rule out TDF-induced nephrotoxicity should be explored, given that there might be a situation where substitution of TDF is not realistically available and TDF needs to be continued in a resource-limited setting.

Our study has several limitations. Because of its cross-sectional nature, it was not possible to identify a causative relationship that TDF induces TD which subsequently develops CKD. Further prospective studies are required to confirm this hypothesis. Second, TD was arbitrarily defined in this study, since for urinary β2MG there is no cut-off value with consensus available. Although greater than 1000 μg/L at both timepoints was set for the definition of TD in this study, the result is still stable even if the value is set at 3000 μg/L or higher. In this regard as well, longitudinal studies are needed to determine the cut-off value of an early marker for TD to prevent possible CKD.

In conclusion, the present study demonstrated higher levels of urinary β2MG in the patients who had been exposed to TDF compared with the patients who had not been exposed to TDF. Furthermore, not only exposure of TDF but also LPV/r was strongly associated with TD and CKD, in addition to known risk factors. This result calls for attention to deliberate monitoring of TD and CKD, especially in patients with very low body weight who are co-administered TDF and LPV/r.

Key points

TDF and LPVr were strongly associated with tubular and renal dysfunction in Vietnamese HIV-infected patients with low body weight. Therefore, second line therapy should be monitored more carefully.

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Author contributions

D.M., N.T., Y.K., H.G., and S.O. did the study design and conception. D.N., T.N., and K.N. collected the data. D. N. and S. M contributed analysis tools. D.M., S.M., D.N and J.T. did the data management and the statistical analyses. D.M. wrote first draft of article with help from D.N., K.N., H.G., and S.O. All authors participated in revising it critically for important intellectual content, and approved the final version for publication.

Conflicts of interest

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V. Appendix

1. List of Participants from Bach Mai Hospital Attending NCGM Training Courses

No	Name	Position	Department	Training course	Duration (days)	Date
1	Dr. Phan Thu Phuong	Doctor	Respiratory Center	Development of bronchoscope technique and spreading related device in Vietnam	2	24/5-25/5
2	Dr. Le Thi Thu Trang	Doctor	Respiratory Center		17	5/6-21/6
3	Dr. Phan Thi Hanh	Doctor	Respiratory Center			5/6-21/6
4	Mr. Pham Trong Dat	Nurse	Respiratory Center			5/6-21/6
5	Mr. Nguyen Huy Tuan	Nurse	Respiratory Center		17	14/8-30/8
6	Mr. Nguyen Anh Tuan	Engineer	Medical Equipment	Project of Surgical Team Approach to Health and Medicine Based on Bach Mai Hospital	5	10/9-14/9
7	Mr. Le Xuan Canh	Engineer	Medical Equipment		5	10/9-14/9
8	Mr. Nguyen Dinh Khanh	Nurse	Intensive Care		5	10/9-14/9
9	Dr. Ta Viet Phuong	Doctor	Neurosurgery	Project of Surgical Team Approach to Health and Medicine Based on Bach Mai Hospital	18	9/10-26/10
10	Dr. Nguyen Thi Kim Lien	Doctor	Rehabilitation		12	15/10-26/10
11	Dr. Nguyen Thi Dung	Doctor	Rehabilitation			15/10-26/10
12	Mr. Nguyen Hai Linh	Occupational Therapist	Rehabilitation			15/10-26/10
13	Mr. Duong Cong Doan	Physical Therapist	Rehabilitation			15/10-26/10
14	Mr. Nguyen Dang Khoa	Nurse	Neurosurgery			15/10-26/10
15	Dr. Pham Van Dung	Doctor	Clinical Nutrition Center			15/10-26/10
16	Ms. Nguyen Thi Thu	Pharmacist	Pharmacy			15/10-26/10
17	Dr. Bui Thi Huong Giang	Doctor	ICU	Project of Surgical Team Approach to Health and Medicine Based on Bach Mai Hospital	8	9/10-16/10
18	Ms. Duong Thi Nguyen	Nurse	ICU			9/10-16/10
19	Dr. Tran Dang Luan	Doctor	Anesthesia			9/10-16/10
20	Mr. Tong Ba Tan	Nurse	Anesthesia			9/10-16/10
21	Dr. La Quy Huong	Doctor		Development of bronchoscope technique and spreading related device in Vietnam	17	9/10-25/10
22	Dr. Nguyen Ngoc Du	Doctor			11	12/11-22/11

2. List of Participants from Other Hospitals Attending NCGM Training Courses

No	Name	Position	Department	Hospital	Training course	Duration (days)	Date
1	Dr. Nguyen Thi Thu Trang	Doctor	Respiratory	Bac Gian General Hospital	Development of bronchoscope technique and spreading related device in Vietnam	2	24/5-25/5
2	Dr. Nguyen Van Duc	Doctor		Tuberculosis and Lung Diseases Hospital		2	24/5-25/5
3	Dr. Hoang Thi Lan Huong	Doctor		Hue central hospital		2	24/5-25/5
4	Dr. Pham Huu Thuong	Doctor		Hanoi Lung Hospital		2	24/5-25/5
5	Dr. Dang Thi Mai Khue	Doctor	Respiratory	Cho Ray Hospital		2	24/5-25/5
6	Dr. Bui Viet Nga	Doctor	Endoscopic	Vietnam National Cancer Hospital		17	10/7-26/7
7	Ms. Bui Thi Trang	Nurse	Endoscopic	Vietnam National Cancer Hospital		17	10/7-26/7
8	Dr. Le Minh Hang	Doctor	Physician General Internal Medicine	Hanoi Medical University Hospital		17	10/7-26/7
9	Dr. Phan Thi Phuong	Doctor		Hue Central Hospital		17	14/8-30/8
10	Ms. Phan Thi My Van	Nurse		Hue Central Hospital		17	14/8-30/8
11	Dr. Ngo Huu Phuong	Dept. Head	Hospital Quality Management	Duc Giang Hospital	Strengthening Management Capability of Nurses for Quality and Safety in Healthcare to Accelerate Hospital-Wide Cooperation in Vietnamese Hospital	12	1/10-12/10
12	Ms. Nguyen Thi Ngoc Dung	Dept. Head	Nursing Department	Duc Giang Hospital		12	1/10-12/10
13	Ms. Le Thi Kim Nhung	Dept. Deputy Head	Quality Management	Viet Duc University Hospital		12	1/10-12/10
14	Mr. Tran Xuan Vy	Staff	General Planning	Quy Hoa National Leprosy & Dermatology Hospital		12	1/10-12/10
15	Ms. Tran Hoang Suong	Nurse	Head of Nurse	Da Nang Hospital for Women and Children		12	1/10-12/10
16	Ms. Nguyen Thi My Linh	Staff	Quality Management	Ba Ria Hospital		12	1/10-12/10
17	Ms. Hoang Thi Ngoc Phuong	Dept. Head	Internal Medicine Section, Nursing Department	Ba Ria Hospital		12	1/10-12/10
18	Ms. Nguyen Thi Tuyet Trinh	Dept. Head	Quality Management	People's Hospital 115		12	1/10-12/10
19	Dr. Do Xuan Hoe	Doctor		Central 74 Hospital	Development of bronchoscope technique and spreading related device in Vietnam	17	9/10-25/10
20	Ms. Ha Thi Phuong	Nurse		Central 74 Hospital		17	9/10-25/10
21	Dr. Tran Minh Tri	Doctor		Ho Chi Minh University of Medicine and Pharmacy		17	9/10-25/10
22	Dr. Nguyen Ngoc Minh Chau	Doctor	Pediatrics	Nationa Hue Central Hospital	Support for Strengthening Medical Treatment Ability of Childhood Cancer in Developing Country	25	29/10-22/11
23	Dr. Nguyen Thi My Linh	Doctor	Pediatrics	Nationa Hue Central Hospital		25	29/10-22/11
24	Dr. Nguyen Thi Da Thao	Doctor	Department of Imagination	Nationa Hue Central Hospital		25	29/10-22/11
25	Dr. Dinh Viet Hung	Doctor		Children Hospital 1		26	12/11-7/12
26	Dr. Vu Manh Hoan	Doctor		Vietnam National Children's Hospital		26	12/11-7/12
27	Dr. Phan Thanh Chinh	Doctor		Hue Central Hospital		26	12/11-7/12
28	Dr. Duong Minh Ngoc	Lecturer		Cho Ray Hospital	Development of bronchoscope technique and spreading related device in Vietnam	11	12/11-22/11

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