

# A Study of Tenofovir Disoproxil Fumarate-Associated Nephrotoxicity in Comparison with Zidovudine in Patients with AIDS in King Chulalongkorn Memorial Hospital

Khobchok Woratanarat, M.D.  
Chusana Suankratay, M.D., Ph.D.

**Background and Rationale:** No prospective controlled study evaluating all renal functions in patients receiving tenofovir disoproxil fumarate (TDF) compared with those receiving other nucleoside analogues has been done. Our study aimed to compare the incidence of all renal dysfunctions in patients receiving TDF and zidovudine (AZT) at King Chulalongkorn Memorial Hospital.

**Methods:** A prospective controlled study evaluating renal functions including creatinine clearance (CrCl) and all tubular functions was conducted in HIV-infected patients receiving either TDF- or AZT-containing HAART regimen from July 2008 to February 2009.

**Results:** Of 51 patients, there were 39 and 12 subjects in TDF and AZT group with 23:16 and 7:5 in the male to female ratio in each group. Coadministration with non-nucleoside reverse transcriptase inhibitor or protease inhibitor was noted in 36 (92.30%) and 3

(7.70%) patients in the TDF group, and 11 (91.67%) and 1 (8.33%) patients in the AZT group, respectively. There was a significant difference in the baseline CD4 cell count in the TDF group compared with the AZT group (359 and 225 cells/mm<sup>3</sup>,  $p = 0.02$ ) and more HAART experienced in the TDF group ( $p = 0.001$ ). There were no significant differences in other baseline characteristics and baseline renal functions. There were no differences in the change of the CrCl collected from 24-hours urine samples between the 2 groups over the follow up period of 6 months ( $p = 0.907$ ). Neither proximal tubulopathy nor distal tubulopathy were observed during the follow-up.

**Conclusion:** This is the first prospective controlled study comparing all renal functions in HIV-infected patients receiving TDF or AZT. No differences in the incidence of renal failure and renal tubular dysfunction between the 2 groups. Long-term follow up is needed.

---

Infectious Diseases Unit, Department of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

Received for publication: June 26, 2009.

**Keywords:** Tenofovir disoproxil fumarate, renal toxicity, HIV-1, Fanconi's syndrome

# Prospective Surveillance of Hospital-Acquired Pneumonia (HAP) and Ventilator-Associated Pneumonia (VAP) in Adults at Siriraj Hospital: Etiology, Clinical Outcomes, and Impact of Antimicrobial Resistance

Peerawong Werarak, M.D.\*,  
Pattarachai Kiratisin, M.D., Ph.D.\*\*,  
Visanu Thamlikitkul, M.D.\*

## Introduction

Nosocomial pneumonia (NP), hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), is an important cause of morbidity and mortality in hospitalized patients. The mortality rate of HAP and VAP is high because the causative agents are usually resistant to antibiotics.

## Objectives

To determine prevalence of bacterial pathogens of HAP and VAP, clinical characteristics, risk factors of HAP and VAP, antimicrobial resistance among major respiratory pathogens, clinical implication of antimicrobial resistance, antimicrobial regimens used and treatment outcome of adult patients with HAP and VAP at Siriraj Hospital.

## Patients and Methods

This was a prospective, hospital-based, active surveillance study on HAP and VAP in hospitalized adults at Siriraj Hospital from December 2007 to March

2009. The patients with HAP and VAP were followed prospectively until they expired or discharged from the hospital.

## Results

One hundred and forty-six adult patients were included. Seventy percent of the patients were males with the mean age of all patients of 70.8 years. HAP was accounted for 24.7 percent and VAP 75.3 percent. Most of the patients (82.9%) had late-onset HAP or VAP with the median of onset of pneumonia of 11 days. Two third of the patients were hospitalized in general medical wards. Bronchopneumonia was observed in 53.4 percent and multilobar pneumonia in 24.7 percent. *A. baumannii* was the most common isolated pathogen and 92.3 percent of them were multidrug-resistant (MDR) or pandrug-resistant (PDR). The other common isolated pathogens were *K. pneumoniae*, *P. aeruginosa* and methicillin-resistant *S. aureus* (MRSA). Carbapenem was the most commonly used initial antibiotic (45.9%) followed

\*Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

\*\*Department of Microbiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

Received for publication: June 26, 2009.

by colistin (21.9%) and cephalosporins (21.1%). The concordance of initial antibiotics was 58.9 percent. Antibiotics were modified 43.8 percent of the patients. Colistin was the most commonly used modified antibiotic followed by carbapenem. The modified antibiotics were concordance with isolated bacteria in 98.4 percent. The patients received mechanical ventilator support in 81.5 percent with the median ventilator day of 10 days. At the initial response at 72 hours, an improvement was 56.8 percent and a mortality rate due to pneumonia was 14.4 percent. Death due to pneumonia at the end of treatment was 42.5 percent. The 30-day mortality from pneumonia was 45.9 percent. There were no significant differences in the outcomes of pneumonia between HAP and VAP. The factors associated with PDR-organisms were late-onset hospital-acquired pneumonia and previous carbapenem usage within 72

hours. Septic shock and bilateral lung involvement were significantly associated with unfavorable outcomes at 72 hours. Septic shock, severe sepsis, and previous carbapenem usage within 72 hours were significantly associated mortality at the end of treatment and at 30 days after developing pneumonia.

### **Conclusion**

HAP and VAP remain to be very important hospital-acquired infections at Siriraj Hospital. The isolated pathogens were usually multidrug-resistant and the mortality rate was still high. The local data on prevalence of the isolated pathogens and their antibiotic susceptibility may help clinicians choose more appropriate initial antibiotics in order to improve the outcome and to decrease the emergence of resistant organisms.

# HLA-B\*4001 Allele is Associated with Lipodystrophy in HIV-infected Thai Patients Who Received Stavudine-containing Antiretroviral Regimen

Wittaya Wangsomboonsiri, M.D.<sup>1</sup>,  
Surakameth Mahasirimongkol, M.D.<sup>4</sup>,  
Soranun Chantarangsu, M.D.<sup>2,5</sup>,  
Sasisopin Kiertiburanakul, M.D.<sup>1</sup>,  
Angkana Charoenyingwattana, M.D.<sup>3</sup>,  
Chupong Thongnak, M.D.<sup>3</sup>,  
Taisei Mushiroda, M.D.<sup>5</sup>,  
Yusuke Nakamura, M.D.<sup>5</sup>,  
Wasun Chantratita, M.D.<sup>2</sup>,  
Somnuek Sungkanuparph, M.D.<sup>1</sup>

## ABSTRACT

**Background:** Stavudine-containing antiretroviral regimens are widely used in Thailand and other developing countries. Stavudine-induced lipodystrophy is commonly observed, however, in only some patients. The aim of this study was to determine the clinical risk factors and HLA alleles associated with stavudine-induced lipodystrophy.

**Methods:** A cross-sectional, step-wise case-control association study was conducted in patients receiving stavudine-containing antiretroviral regimens. Clinical assessment for lipodystrophy by physical examination, anthropometry, bioelectrical impedance analysis, DEXA scans and blood test for lipid profile were obtained. Genotypic HLA-A, HLA-B, HLA-C, HLA-DRB1,

HLA-DQB1, and HLA-DPB1 were verified. HLA allele that had a possible association with stavudine-induced lipodystrophy were determined.

**Results:** There were 103 patients; 55 in case group (moderate to severe lipodystrophy) and 48 in control group (absent to mild lipodystrophy). Baseline characteristics between two groups were similar except for AIDS-defining illness and undetectable viral load. Anthropometric data, bioelectrical impedance analysis and DEXA scan revealed the significantly lower regional body fat and body fat mass in case group. By forward stepwise logistic regression, The presence of HLA-B\*4001 [OR=14.05; 95%CI, 2.58-76.59; p=0.002] and longer duration of stavudine treatment [OR=1.02; 95%CI, 1.00-1.04; p=0.02) were significantly

<sup>1</sup>Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

<sup>2</sup>Department of Pathology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

<sup>3</sup>Pharmacogenomics Project Under Collaboration between Thailand Center of Excellence for Life Sciences, Mahidol University, Bangkok 10400, Thailand.

<sup>4</sup>Center for International, Cooperation and Medical Genetic Section, Department of Medical Sciences, Ministry of Public Health, Nonthaburi 11000, Thailand.

<sup>5</sup>Research Group for Pharmacogenomic, RIKEN, Center for Genomic Medicine, Tokyo, Japan.

associated with stavudine-induced lipodystrophy while higher BMI during treatment [OR=0.73; 95% CI, 0.61-0.86;  $p<0.001$ ) was associated with lower risk for lipodystrophy. HLA-B\*4001 has high specificity (95.8%) and positive predictive value (88.9%) for lipodystrophy.

**Conclusions:** HLA-B\*4001 is a strong factor associated with lipodystrophy. It is possible to use the HLA-B\*4001 as a genetic marker to predict patients who may have stavudine-induced lipodystrophy in order to avoid or shorten the duration of stavudine use.

# Therapeutic Equivalence of Generic Imipenem/Cilastatin for Therapy of Infections at Siriraj Hospital

Sukij Piyasirisilp, M.D.,  
Wanna Premprawat, M.D.,  
Visanu Thamlikitkul, M.D.

**Background:** Several generic imipenem/cilastatin formulations have been approved by Thai FDA and a generic imipenem/cilastatin (Yungjin<sup>R</sup>) has been available in Siriraj Hospital since 2007. Since imipenem/cilastatin is usually given to the patients with serious hospital-acquired infections, the generic imipenem/cilastatin must be therapeutically equivalent to the original imipenem/cilastatin.

The objective of the study was to compare effectiveness and safety of generic imipenem/cilastatin with original imipenem/cilastatin for therapy of infections in hospitalized patients at Siriraj Hospital.

**Methods:** Medical records of adult hospitalized patients at Siriraj Hospital who received imipenem/cilastatin at least 48 hours during June 2007 to September 2008 were reviewed. The effectiveness data of 300 patients who received original imipenem/cilastatin were compared with those of 300 patients who received generic imipenem/cilastatin in order to determine if a difference in composite favorable outcome of both formulations was within 10 percent.

**Results:** The demographics, clinical features of infections, site of infections, type of causative organisms and concomitant antibiotics of the patients in both groups were not significantly different. The overall favorable

outcomes in the original imipenem/cilastatin and the generic imipenem/cilastatin groups were 65 percent and 58.7 percent respectively (absolute difference 6.3%, 95% CI -1.4% to 14%). Cure rates of infections in the original imipenem/cilastatin and the generic imipenem/cilastatin groups were 35 percent and 28.7 percent respectively (absolute difference 6.3%, 95% CI -1.1% to 13.7%). Super-infection rates in the original imipenem/cilastatin and the generic imipenem/cilastatin groups were 4.7 percent and 9 percent respectively (absolute difference -4.3%, 95% CI -8.5% to 0.3%). Mortality due to infections in the original imipenem/cilastatin and the generic imipenem/cilastatin groups were 18.3 percent and 21.3 percent respectively (absolute difference -3%, 95% CI -9.4% to 3.4%). Overall mortality in the original imipenem/cilastatin and the generic imipenem/cilastatin groups were 35.3 percent and 43 percent respectively (absolute difference -7.7%, 95% CI -15.3% to 0.1%). The occurrence of adverse events in the patients in both groups was not significantly different.

**Conclusion:** Although the point estimate of composite favorable outcome of the patients who received generic imipenem/cilastatin (Yungjin<sup>R</sup>) is <10 percent of those who received original imipenem/cilastatin (Tienam<sup>R</sup>), generic imipenem/cilastatin seems to be inferior to

original imipenem/cilastatin because the upper limits of 95 percent confidence interval of differences of several important clinical outcomes are more than 10 percent.

# Survival of Dengue Virus in Blood, Urine, Saliva and Buccal Mucosa in Complete Recovery Patients

Chalinee Laosakul, M.D.

Wanla Kulwichit, M.D.

**Background:** we demonstrate the existence of live dengue virus detected by RT-PCR in blood and urine even in late postfebrile period. The virus is isolated by mosquito inoculation using urine from acutely-infected patients as late as 28 days after the onset of illness.

**Methods:** Dengue infection patients was based on the standard serum ELISA assay. Blood and urine specimens were collected during fever and postfebrile period in 2 phases (Early and late defervescence phase) for testing by dengue-specific PCR and ELISA assay. In positive cases blood and urine specimen were processed and then employed for *Aedes aegypti* intrathoracic inoculation. Surviving mosquitoes were dissected 14 days after inoculation and dengue-specific PCR was performed on extracts from the body parts

of injected mosquitoes by pooled RT-PCR .

**Results:** We enrolled 25 patients with dengue infection and 13 negative controls. Dengue viruses were detected in blood and urine 21 percent and 33.3 percent respectively by dengue - specific PCR as late as 46 days after onset of illness. Live dengue viruses were successful isolation in urine specimen by pooled RT-nested PCR after mosquito inoculation in late defervescence as late as 24 days.

**Conclusions:** DENV was isolated by mosquito inoculation from urine of late convalescent phase of infection. These findings have pathologic and epidemiologic significances the potential role of urine in the transmission of disease through contaminated urine with help from arthropod vector.

# Hepatitis B Virus Drug Resistance In HIV-Infected Patients Taking Lamivudine-Containing Antiretroviral Therapy

Pawinee Wongprasit, M.D.<sup>1</sup>,  
Weerawat Manosuthi, M.D.<sup>1,2</sup>,  
Somnuek Sungkanuparph, M.D.<sup>1</sup>

## ABSTRACT

**Background:** HIV and HBV co-infection is common in Asia. Lamivudine (3TC) had been widely used as a part of antiretroviral therapy (ART) for HIV infection while tenofovir (TDF) was not available. This study aimed to determine the prevalence and risk factors of HBV drug resistance (HBV DR) in HIV infected patients receiving 3TC-containing ART.

**Methods:** A cross-sectional study was conducted in HBV/HIV co-infected patients who received 3TC-containing ART and had undetectable HIV RNA. HBV DNA and HBV genotypic resistance test were performed. Patients were categorized into 2 groups: with and without HBV DR.

**Results:** There were 84 patients (mean age, 42.2 ± 10.2 years, 77% male). Median (range) duration of ART and 3TC use was 46 (2-177) and 40 (3-140) months, respectively. Median (range) CD4 was 352 (49-790) cells/mm<sup>3</sup>. Of 84 patients, 19 (23%) had HBV DR with a median (range) HBV DNA of 2.56x10<sup>7</sup> (2,540-11x10<sup>7</sup>) IU/mL. In univariate analysis, there

were no differences of age, gender, ART regimen, liver function test, anti-HBc, anti-HCV between 2 groups ( $p > 0.05$ ). Patients with HBV DR had a higher proportion of positive HBeAg (68.4% vs 3.8%,  $p < 0.001$ ). In multivariate analysis, positive HBeAg [Odds ratio (OR) = 16.64; 95% CI, 3.31-83.60,  $p < 0.001$ ] and duration of 3TC [OR = 1.045; 95% CI, 1.001 - 1.092,  $p = 0.046$ ] were significant risk factors for HBV DR. Of 19 patients with HBV DR, all had 3TC resistance with the mutations as follows: M204V/I (95%), L180M/A181T (95%), L80V/I (47%), V173L (32%), and N236T (21%). Of 19 patients, 95 percent, 84 percent, and 84 percent had HBV DR to telbivudine, entecavir, and adefovir, respectively.

**Conclusions:** HBV DR is common in HBV/HIV co-infected patients receiving 3TC-containing ART without TDF. Positive HBeAg and longer duration of 3TC use are risk factors for HBV DR. In addition to 3TC resistance, cross-resistance to other anti-HBV drugs is also frequently observed.

<sup>1</sup>Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

<sup>2</sup>Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health, Nonthaburi 11000, Thailand.

Received for publication: June 26, 2009.

**Keywords:** HIV, HBV, lamivudine, resistance, mutations

# Adverse Effects of Antiretroviral Agents in HIV-infected patients at Phramongkutklo Hospital

**Worawan Samritmanoporn, M.D.\*,  
Danabhand Phiboonbanakit, M.D.\*,  
Kitti Trakulhun, M.D.\***

**Background:** Chronic Human immunodeficiency virus (HIV)-infected patients who were candidates to receive antiretroviral therapy (ART) need to continue the treatment life-long, thus adverse events (AEs) might be inevitable.

**Objective:** To examine the incidences of clinical and laboratory AEs from antiretroviral agents in HIV-infected patients receiving the treatment at Phramongkutklo Hospital.

**Methods:** Patients' characteristics and AEs occurred in 569 HIV-infected patients treated at an infectious diseases clinic between 1 July, 2008 and 31 Dec, 2008 were studied by a retrospective, observational study.

**Results:** A total of 569 charts were reviewed. Nearly 70 percent of the subjects were males, age range from 17 to 85 years (median = 43 years). Almost all of patients received non-nucleoside

reverse transcriptase inhibitors (NNRTIs)-based regimen (95.6%). The most commonly used nucleoside/ nucleotide reverse transcriptase inhibitors (NRTIs) backbone were stavudine and lamivudine (83.3 and 98.2%, respectively). The overall incidences of clinical AEs, grade 1-2 and grade 3-4 laboratory AEs were 42.4, 57.82, and 22.31 percent, respectively. The most common clinical AEs were lipodystrophy (21.9%) especially in patients who received stavudine. Rash was developed in 11.75 percent of the patients. Changing of regimens was required in most of the patients who developed rash. While the most common laboratory AEs were dyslipidemia, the most frequent laboratory AEs that forced the patients to discontinue ART were hematologic abnormalities.

**Conclusions:** At Phramongkutklo Hospital, ART-related clinical and laboratory AEs are not uncommon and lead to interrupt or change ART regimens in a considerable number of the patients.

---

\*Division of Infectious Diseases, Department of Medicine, Phramongkutklo Hospital, Bangkok 10400, Thailand.

Received for publication: June 26, 2009.