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Background : *Drug transporters including ABCC2, ABCC4, ABCC10 and SLC22A6 play important roles in regulating physiologic solute and fluid balance in the cell. They also involve in drug delivery into the organs. Therefore, genetic variations of these transporters may influence the pharmacokinetics of drugs and major pharmacological active metabolites. The information of transporter gene polymorphisms can be useful as guidance for the study of the association between genetic variations and pharmacokinetics of drugs.*

Objective : *To determine the allele frequency of ABCC2, ABCC4, ABCC10 and SLC22A6 in Thai HIV - infected patients.*

Research design : *Cross-sectional study.*

Setting : *The HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT), Bangkok, Thailand.*

Patients : *The study enrolled 400 Thai HIV - infected patients from the HIV - NAT from January 1st to September 1st, 2012.*

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Methods : *Nine single nucleotide polymorphisms (SNPs) including ABCC2-24C>T; 1249G>A; 3563T>A; 3972C>T, ABCC4 3463A>G; 4131T>G, ABCC10 526G>A; 2759T>C and SLC22A6 728G>A were investigated. The genotyping was performed by Taqman allelic discrimination assays with fluorogenic probes. All reactions were analyzed by Applied Biosystems 7500 Real-Time PCR System. The deviation of polymorphisms according to Hardy-Weinberg equilibrium was tested using Chi-square test. The comparisons of the allele frequencies between Thai and other populations were performed using Chi-square tests.*

Results : *The allele frequencies of ABCC2 -24C>T; 1249G>A; 3563T>A; 3972C>T, ABCC4 3463A>G; 4131T>G, ABCC10 526G>A and 2759T>C in this population were 21.8%, 7.8%, 0.1%, 24.9%, 19.8%, 49.2%, 51% and 7.1%, respectively. The polymorphism of SLC22A6 728G>A was not found in this population.*

Conclusion : *The prevalence of the polymorphisms examined in this study was similar to those observed among Asian populations. However, they were different from the Caucasian and African populations. The influence of these polymorphisms on pharmacokinetics requires further investigation.*

Keywords : *ABCC2, ABCC4, ABCC10, SLC22A6, polymorphisms, allele frequencies, Thai.*

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ศิวพร มิตรรัก, อัญชลี อวิหิงสานนท์, บราลี ปัญญาวุธโธ. ภาวะพหุสัณฐานของยีน *ABCC2, ABCC4, ABCC10* และ *SLC22A6* ในผู้ป่วยชาวไทยที่ติดเชื้อเอชไอวี. จุฬาลงกรณ์เวชสาร 2557 พ.ย. – ธ.ค.; 58(6): 599 – 611

เหตุผลของการทำวิจัย : *ABCC2, ABCC4, ABCC10 และ SLC22A6 เป็นยีนที่ทำหน้าที่ในการนำส่งยา และมีบทบาทสำคัญในการควบคุมตัวถูกละลายในกระบวนการทำงานของอวัยวะต่าง ๆ ในร่างกายของสิ่งมีชีวิต และควบคุมความสมดุลของของเหลวในเซลล์ นอกจากนี้ยังเกี่ยวข้องกับการนำส่งยาเข้าไปยังอวัยวะต่าง ๆ ดังนั้นความผันแปรทางพันธุกรรมของยีนที่นำส่งยาเหล่านี้อาจมีผลต่อเภสัชจลนศาสตร์ของยาและเมแทบอไลต์ที่ออกฤทธิ์ในทางเภสัชวิทยา ซึ่งข้อมูลภาวะพหุสัณฐานของยีนที่นำส่งยาเหล่านี้จะเป็นประโยชน์ในการใช้เป็นแนวทางในการศึกษาความสัมพันธ์ระหว่างความผันแปรทางพันธุกรรมและ*

: *เภสัชจลนศาสตร์ของยาต่อไป*

วัตถุประสงค์ *ศึกษาความถี่ของแอลลีลของยีน ABCC2, ABCC4, ABCC10 และ SLC22A6 ในผู้ป่วยชาวไทยที่ติดเชื้อเอชไอวี*

รูปแบบการวิจัย : *การศึกษาภาคตัดขวาง*

สถานที่ทำการศึกษา : *ศูนย์ประสานความร่วมมือระหว่าง ไทย ออสเตรเลีย เนเธอร์แลนด์ เพื่อการศึกษาวิจัยทางคลินิกด้านโรคเอดส์ (HIV - NAT)*

ตัวอย่างและวิธีการศึกษา : *ผู้ป่วยชาวไทยติดเชื้อเอชไอวีจำนวน 400 คนที่เข้ารับการรักษา ณ ศูนย์ประสานความร่วมมือระหว่าง ไทย ออสเตรเลีย เนเธอร์แลนด์ เพื่อการศึกษาวิจัยทางคลินิกด้านโรคเอดส์ระหว่างวันที่ 1 มกราคม 2555 ถึงวันที่ 1 กันยายน 2555 ทำการตรวจภาวะพหุสัณฐานของยีน ABCC2 -24C>T; 1249G>A; 3563T>A; 3972C>T, ABCC4 3463 A>G; 4131T>G, ABCC10 526G>A; 2759T>C และ SLC22A6 728G>A ด้วยวิธี Taqman allelic discrimination assays โดยใช้ fluorogenic probes และวิเคราะห์ผลโดย Applied Biosystems 7500 Real-Time PCR System ทดสอบการกระจายตัวของจีโนไทป์ตามกฎของ Hardy - Weinberg equilibrium และเปรียบเทียบความถี่ของแอลลีลของแต่ละยีนระหว่างประชากรชาวไทยกับเชื้อชาติอื่นโดยสถิติไคว์สแคว์*

ผลการศึกษา : *ความถี่ของแอลลีลของยีน ABCC2 -24C>T; 1249G>A; 3563T>A; 3972C>T, ABCC4 3463 A>G; 4131T>G, ABCC10 526G>A และ 2759T>C เท่ากับ 21.8%, 7.8%, 0.1%, 24.9%, 19.8%, 49.2%, 51% และ 7.1% ตามลำดับ แต่ไม่พบภาวะพหุสัณฐานของยีน SLC22A6 728G>A ในผู้ป่วยกลุ่มที่ทำการศึกษา*

สรุป : *ความชุกของภาวะพหุสัณฐานของยีนที่ทำการศึกษาในประชากรไทยมีความใกล้เคียงกับความชุกของประชากรกลุ่มอื่นในเอเชีย แต่พบว่ามีความแตกต่างกับชาวคอเคเซียนและชาวแอฟริกา แต่อย่างไรก็ตามควรมีการศึกษาเพิ่มเติมถึงผลของภาวะพหุสัณฐานของยีนเหล่านี้ต่อเภสัชจลนศาสตร์ของยาต่อไป*

คำสำคัญ : *ABCC2, ABCC4, ABCC10, SLC22A6, ภาวะพหุสัณฐาน, ความถี่ของ แอลลีล, ไทย.*

Pharmacogenomics plays an important role in identifying responders and non-responders, avoiding adverse events, and optimizing drug doses.[1] The inter – individual variation in drug responses among patients is a concern in pharmacotherapy. The inter – individual variability in drug responses could be due to multiple factors including disease status, patient characteristics, genetic and environmental factors. Genetic variants can influence the activity of enzymes or transporters which may affect pharmacokinetics and major pharmacologically active metabolites. This could lead to differences in drug efficacy and safety among patients.[2]

The process of drug delivery into the body requires transporters such as organic anion transporter 1 (OAT1), multidrug resistance-associated protein 2 (MRP2), multidrug resistance -associated protein 4 (MRP4) and multidrug resistance - associated protein 7 (MRP7). Drug transporters are expressed in various tissues including the liver, brain, intestine and kidney. It is widely accepted that some drug transporters may be involved in the characteristics of pharmacokinetics of the drugs, i.e., intestinal absorption, tissue distribution, liver and kidney elimination.[3-5]

The organic anion transporter 1 (OAT1) is a protein encoded by the *SLC22A6* gene in human.[6,7] It is a transmembrane protein which mainly expresses in the basolateral membrane of proximal tubular cells of the kidneys. In the proximal tubule, OAT1 is responsible for an uptake of a wide range of hydrophilic organic anions from plasma into the cytoplasm of the proximal tubular cells of the kidneys. Known substrates of OAT1 include diuretics, ACE inhibitors, antiviral agents, beta-lactam antibiotics, antineoplastics, and NSAIDs.[8]

Multidrug resistance - associated protein 2 (MRP2) is a protein encoded by the *ABCC2* gene. MRP2 is mainly expressed in the liver and kidneys. It is localized in the apical surface, predominantly in the canalicular membrane of hepatocytes. Moreover, it is presented in the brush-border membrane of renal proximal tubules. This indicates the potential role of this transporter in the excretion of drugs from the renal epithelial cells into urine across the apical membrane. Known substrates of MRP2 include vinblastine, tenofovir, and methotrexate.[9 - 11] Multidrug resistance-associated protein 4 (MRP4) is a protein encoded by the *ABCC4* gene. MRP4 is expressed in the basolateral membrane and the apical membrane of the renal proximal tubule cells. MRP4 is involved in the efflux of cyclic nucleotides and some nucleoside monophosphate analogues, including nucleoside - based antiviral drugs.[11,12] Multidrug resistance-associated protein 7 (MRP7) is a protein encoded by the *ABCC10* gene which is expressed in the liver, brain, colon and kidneys. Its substrates include docetaxel, gemcitabine and cytarabine.[10,13]

Genetic variations of drug transporters are one of the important factors contributing to the variability of drugs' pharmacokinetics. Previous studies reported an association between *ABCC2* polymorphisms and methotrexate plasma levels.[14,15] Moreover, there is also evidence of the association between the genetic variations of drug transporters and toxicity. An association between drug transporter genes and the risk of kidney tubular dysfunction (KTD) was demonstrated in patients receiving tenofovir.[11-13,16] Therefore, the information of genetic polymorphisms of drug transporters could

be useful for determining the variability in drug concentrations and toxicity.

The polymorphisms of *SLC22A6, ABCC2, ABCC4* and *ABCC10* have been investigated in various populations.[16 - 18] However, the information is lacking in the Thai population. As the polymorphisms of drug transporters may affect pharmacokinetics of several drugs, an investigation of the genetic variants of these transporters can drive an understanding of the inter – individual variability in drug absorption, distribution, metabolism, and excretion. Therefore, this study is aimed to determine the allele frequency of *SLC22A6*, *ABCC2, ABCC4* and *ABCC10* in Thai patients.

Patients and Methods

Patients

The study included 400 Thai HIV-infected patients from the HIV Netherlands Australia Thailand Research Collaboration (HIV - NAT) during January 1st to September 1st, 2012. The study protocol has been approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. Informed consents were obtained from all patients participating in the study.

Pharmacogenetic analyses

Human genomic DNA was extracted from peripheral blood mononuclear cells (PBMC) by QIAamp®DNA Blood Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instruction. Nine single nucleotide polymorphisms (SNPs), including *ABCC2*-24C>T (rs717620), *ABCC2* 1249G>A (rs2273697), *ABCC2* 3563T>A (rs17222723), *ABCC2* 3972C>T (rs3740066), *ABCC4* 3463A>G (rs1751034), *ABCC4* 4131T>G (rs3742106), *ABCC10* 526G>A (rs9349256), *ABCC10* 2759T>C (rs2125739) and *SLC22A6* 728G>A (rs11568626) were investigated. The genotyping was performed by Taqman allelic discrimination assays with fluorogenic probes (Applied Biosystems, Foster City, CA). The probes for all 9 SNPs were designed by Applied Biosystems and were presented in Table 1. All reactions were analyzed by Applied Biosystems 7500 Real-Time PCR System.

Table 1. Context sequence of *ABCC2, ABCC4, ABCC10* and *SLC22A6* polymorphisms.

Gene	SNPs	Context Sequence [VIC/FAM]
ABCC2	-24C>T	ACAATCATATTAATAGAAGAGTCTT[C/T]GTTCCAGACGCAGTCCAGGAATCAT
	1249G>A	CAACTTGGCCAGGAAGGAGTACACC[A/G]TTGGAGAAACAGTGAACCTGATGTC
	3563T>A	CAGCGATTTCTGAAACACAATGAGG[A/T]GAGGATTGACACCAACCAGAAATGT
	3972C>T	TCCTCAGAGGGATCACTTGTGACAT[C/T]GGTAGCATGGAGAAGGTAGGTGGAG
ABCC4	3463A>G	TGCATACCTGAGGTATGATTGACAT[G/A]TTCTTCCTTAAATCGTGAAGTCCAA
	4131T>G	GTTTACATAGTCCAAAAACTAGTGG[T/G]AAATGCCTTCGGAACGGACTTGACA
ABCC10	526G>A	GAGTTTTCACTCTCTCCTGACCTTT[A/G]TCCAACCCTGTGCCCCACAGCTCAA
	2759T>C	ACAGCCCCCTCCTCACCACCCAGCA[C/T]CCCAGTGTTCCCACTGCCCAAAGCT
SLC22A6	728G>A	GCTGAGGTTGGCATCGGCAGGCGGG[G/A]GGCAGTGGTGGGTAGGGATGGCAGC

Statistical analysis

Genotype frequencies were determined by direct counting. The genotypes were divided into three groups, named: wild-type (two copies of common allele), heterozygous (one copy of the variant allele) and homozygous (two copies of the variant allele). The deviation from Hardy-Weinberg equilibrium was determined by Chi-square test. Allele frequencies were compared between populations using Chi-square test. All statistical analyses were performed using the Statistical Package for Social Sciences software (SPSS version 17, SPSS Co., Ltd., Bangkok Thailand). The level of significance was set at 0.05.

Results

Of the 400 patients enrolled in this study, 180 patients were female (45%) and 220 male (55%). The average age (± standard deviation) of participants was 43.47 ± 7.85 years. The summary of the patients' characteristics is presented in Table 2.

Table 2. Demographic data of patients enrolled the study. (n = 400 patients)

Characteristics	**Frequency (mean ± S.D.)**	**% (range)**
Gender - female	180	45
- male	220	55
Age (years)	(43.47 ± 7.85)	(22 - 71)
Weight	(60.31 ± 12.12)	(37.6 - 117.7)
ARV regimen*		
- 3TC+ATV+RTV+TDF	35	8.75
- 3TC+ATV+RTV+TDF+ZDV	1	0.25
- 3TC+DRV+RTV+TDF	14	3.5
- 3TC+EFV+TDF	104	26
- 3TC+LPV+RTV+TDF	39	9.75
- 3TC+NVP+TDF	53	13.25
- 3TC+RTV+SQV+TDF	55	13.75
- ATV+FTC+TDF+RTV	4	1
- ATV+RTV+TDF+ZDV	1	0.25
- DRV+FTC+TDF+RTV	1	0.25
- EFV+FTC+TDF	33	8.25
- EFV+TDF+ZDV	8	2
- FTC+TDF+LPV+RTV	11	2.75
- FTC+TDF+RTV+SQV	31	7.75
- LPV+RTV+TDF+ZDV	6	1.5
- NVP+TDF+ZDV	2	0.5
- RTV+SQV+TDF+ZDV	2	0.5

*ATV (Atazanavir), DRV (darunavir), EFV (Efavirenz), FTC (emtricitabine), 3TC (Lamivudine), LPV (Lopinavir), NVP (Nevirapine), RTV (Ritronavir), SQV (Saquinavir), TDF (Tenofovir), ZDV (Zidovudine)

The results from SNPs analysis showed the frequencies of the heterozygous genotype of *ABCC2* -24C>T; 1249G>A; 3563T>A; 3972C>T, *ABCC4* 3463A>G; 4131T>G, *ABCC10* 526G>A and 2759T>C were 33%, 13.5%, 0.2%, 35.2%, 31.5%, 48%, 54% and 12.8% respectively. The frequencies of the homozygous genotype of *ABCC2* -24C>T; 1249G>A; 3972C>T, *ABCC4* 3463A>G; 4131T>G, *ABCC10* 526G>A and 2759T>C were 5.2%, 1%, 7.3%, 4%, 25.2%, 24% and 0.7% respectively. The variant of *SLC22A6* 728G>A was not found in this population. Therefore, the allele frequencies of *ABCC2*-24C>T; 1249G>A; 3563T>A; 3972C>T, *ABCC4* 3463A>G; 4131T>G, *ABCC10* 526G>A,2759T>C, and *SCL22A6* 728G>A were 21.8%, 7.8%, 0.1%, 24.9%, 19.8%, 49.2%, 51%, 7.1% and 0%, respectively. All polymorphisms were in Hardy-Weinberg equilibrium (P>0.05). The genotype frequencies of *ABCC2, ABCC4, ABCC10* and *SLC22A6* genes are shown in Table 3.

Table 3. Genotype frequencies of *ABCC2, ABCC4, ABCC10* and *SLC22A6* in Thai patients. (n = 400)

Gene (Protein)	Polymorphisms (SNP identification)	Genotype	Frequency	%	P value*
ABCC2 (MRP2)	1249G>A (rs2273697)	GG	342	85.5	0.264
		AG	54	13.5	
		AA	4	1.0	
	-24C>T (rs717620)	CC	247	61.8	0.542
		CT	132	33.0	
		TT	21	5.2	
	3563T>A (rs17222723)	TT	399	99.8	0.980
		TA	1	0.2	
		AA	0	0.0	
	3972C>T (rs3740066)	CC	230	57.5	0.255
		CT	141	35.2	
		TT	29	7.3	
ABCC4 (MRP4)	3463A>G (rs1751034)	AA	258	64.5	0.900
		GA	126	31.5	
		GG	16	4.0	
	4131T>G (rs3742106)	TT	107	26.8	0.426
		TG	192	48.0	
		GG	101	25.2	
ABCC10 (MRP7)	526G>A(rs9349256)	GG	88	22.0	0.108
		GA	216	54.0	
		AA	96	24.0	
	2759T>C(rs2125739)	TT	346	86.5	0.464
		TC	51	12.8	
		CC	3	0.7	

Table 3. Genotype frequencies of *ABCC2, ABCC4, ABCC10* and *SLC22A6* in Thai patients. (n = 400) (Continue)

Gene (Protein)	Polymorphisms (SNP identification)	Genotype	Frequency	%	P value*
SLC22A6 (OAT1)	728G>A (rs11568626)	GG	400	100.0	-
		GA	0	0.0	
		AA	0	0.0	

*Test for Hardy-Weinberg Equilibrium, Chi-square test

The comparison of the allele frequencies of *ABCC2, ABCC4, ABCC10* and *SLC22A6* between Thai population and those previously reported from other populations are shown in Table 4. The results showed that the allele frequencies of *ABCC2* in this population were similar to those observed in other Asian populations. However, the allele frequencies of *ABCC2* 1249G>A; 3563T>A; and 3972C>T in this population were lower than those reported in Caucasian population (7.8% *vs*. 23.3%, 0.1% *vs*. 6.7%, and 24.9% *vs*.38%, respectively).[17,18] As for *ABCC4*, the allele frequency of *ABCC4* 3463A>G was lower than those reported in Japanese population (19.8% *vs*. 34.3%), whereas the frequency of *ABCC4* 4131T>G was significantly higher than the frequency observed in the African population (49.2% vs. 34.9%).[17] The allele frequency of *ABCC10* 526G>A and *ABCC10* 2759T>C were similar among Asian populations, but they were significantly different from African and Caucasian populations.[17]

Table 4. Comparison of *ABCC2, ABCC4, ABCC10* and *SLC22A6* allele frequencies between Thai and other populations.

Gene (Protein)	Polymorphisms (SNP identification)	Ethnicity	Sample Size	Allele frequency (%)		P value*
ABCC2 (MRP2)	-24C>T (rs717620)			C	T	
		Thai (This study)	400	78.2	21.8	
		Chinese[17]	168	78.6	21.4	0.863
		Mexican[17]	154	75.3	24.7	0.617
		European[17]	330	80.3	19.7	0.728
	1249G>A (rs2273697)			G	A	
		Thai (This study)	400	92.2	7.8	
		Japanese[16]	190	86.0	14.0	0.175
		Chinese[17]	168	89.9	10.1	0.621
		Mexican[17]	154	87.0	13.0	0.249
		European[17]	330	76.7	23.3	0.003

Table 4. Comparison of *ABCC2, ABCC4, ABCC10* and *SLC22A6* allele frequencies between Thai and other populations. (Continue)

Gene (Protein)	Polymorphisms (SNP identification)	Ethnicity	Sample Size	Allele frequency (%)		P value*
	3563T>A (rs17222723)			T	A	
		Thai (This study)	400	99.9	0.1	
		Asian[18]	90	100.0	0.0	0.943
		African[18]	76	93.8	6.2	0.054
		Caucasian[18]	60	93.3	6.7	0.030
	3972C>T (rs3740066)			C	T	
		Thai (This study)	400	75.1	24.9	
		Japanese[17]	88	71.6	28.4	0.631
		Chinese[17]	90	73.3	26.7	0.747
		Caucasian[18]	46	62.0	38.0	0.048
ABCC4	3463A>G (rs1751034)			A	G	
(MRP4)		Thai (This study)	400	80.2	19.8	
		Japanese[17]	172	65.7	34.3	0.026
		Chinese[17]	166	81.9	18.1	0.718
		African[17]	166	78.3	21.7	0.728
		European[17]	330	86.7	13.3	0.182
	4131T>G (rs3742106)			T	G	
		Thai (This study)	400	50.8	49.2	
		Chinese[17]	168	46.4	53.6	0.479
		African[17]	166	65.1	34.9	0.045
		Caucasian[18]	46	58.0	42.0	0.320
ABCC10	526G>A(rs9349256)			G	A	
(MRP7)		Thai (This study)	400	49.0	51.0	
		Japanese[16]	190	38.4	61.6	0.117
		Chinese[17]	166	40.4	59.6	0.200
		African[17]	166	91.6	8.4	<0.001
		European[17]	328	54.3	45.7	0.479
	2759T>C(rs2125739)			T	C	
		Thai (This study)	400	92.9	7.1	
		Japanese[16]	190	86.6	13.4	0.157
		Chinese[17]	168	94.0	6.0	0.774
		African[17]	166	71.7	28.3	<0.001
		Caucasian[18]	66	63.6	36.4	<0.001
SLC22A6	728G>A (rs11568626)			G	A	
(OAT1)		Thai (This study)	400	100.0	0.0	
		African[18]	59	93.2	6.8	0.614

*Chi-square test

Discussion

Drug transporters are expressed in many tissues such as the intestine, liver, kidney, and brain. They play an important role in drug absorption, distribution and excretion. Genetic variants of these transporters can affect pharmacokinetics and major pharmacologically active metabolites which may lead to the difference in drug efficacy and safety among patients. An understanding of genetic variants of drug transporter genes could result in a better approach for optimal drug therapy.

The polymorphisms of *ABCC2, ABCC4, ABCC10*, and *SCL22A6* are reported to be different among the populations.[16 - 18] This study investigated the prevalence of *ABCC2* -24C>T; 1249G>A; 3563T>A; 3972C>T, *ABCC4* 3463A>G; 4131T>G, *ABCC10* 526G>A; 2759T>C and *SLC22A6* 728G>A in Thai HIV - infected patients. The prevalence of genetic polymorphisms examined in this study was comparable to those observed in other Asian populations, except *ABCC4* 3463A>G. Interestingly, the polymorphism of *ABCC4*3463A>G was found to be different among Asian populations. The allele frequency of *ABCC4* 3463A>G observed in this population is similar to the frequency found in the Chinese population (19.8% *vs*. 18.1%),[17] but it was significantly lower than that found in the Japanese population (19.8% *vs*. 34.3%). However, this difference could be due to a small sample size of the Japanese population in the study.

Comparing with the Caucasian population, the allele frequencies of *ABCC2* 1249G>A; 3563T>A; 3972C>T and *ABCC10* 2759T>C found in the Caucasian populations were higher than those found in this Thai population. On the other hand, the allele frequencies of *ABCC4* 4131T>G and *ABCC10* 526G>A found in African population were lower than those observed in this study.

The difference of the polymorphisms of drug transporters may partly explain inter - individul variability in pharmacokinetics, pharmacodynamics and toxicity. A previous study in the Japanese population found the polymorphisms of *ABCC2*-24C>T and *ABCC2* 1249G>A associated with kidney tubular dysfunction in tenofovir - treated patients.[16] A study by Nishijima T *et al.* reported that patients carrying *ABCC2* -24CC and *ABCC2* 1249AA have a higher risk of tenofovir induced KTD.[16] Moreover, an association of two *ABCC10* variants (rs9349256 and rs2125739) and tenofovir-induced KTD was observed.[13] As the polymorphisms of these genetic variants were presented in the Thai population and the screening of these polymorphisms were not performed in clinical practice, a close monitoring of renal function is warranted in all patients receiving tenofovir.

Moreover, genetic variation is one of the major factors contributing to the variability of the pharmacokinetics. A study by Rau T *et al,* [14] found a 2-fold higher of the mean area under the curve from 36 to 48 hours after starting the infusion in female patients carrying at least one mutation allele of *ABCC2* -24T compared with other groups of patients. Moreover, the association of genetic variation of *ABCC2* 3972C>T and methotrexate plasma levels was observed.[15] As the polymorphisms of *ABCC2* -24C>T and 3972C>T are observed in the Thai population, side effects from the drugs that are substrates of these polymorphisms should be aware of in carriers of these genetic variants possibly due to higher drug level.

Conclusion

This is the first study to determine the allele frequencies of *ABCC2, ABCC4, ABCC10* and *SLC22A6* gene in the Thai population. The results revealed the difference of the genetic polymorphisms among the HIV – infected populations. The results from this study can be used as early information for understanding of genetic variants in drug transporters that guides the study of the association between genetic variations and pharmacokinetics/ pharmacodynamics of drugs.

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