ความสัมพันธ์ระหว่างยีน HLA-B*4001 กับการเกิด lipodystrophy ในผู้ป่วยติดเชื้อ HIV ที่ได้รับยา stavudine: การทบทวนวรรณกรรมอย่างเป็นระบบและการวิเคราะห์เชิงอภิมาน

วิมลฉัตร ตั้งอมรสุขสันต์ [1], อรรัตน์ โลหิตนาวี [2] และมนุพัศ โลหิตนาวี [3*]

Association Between HLA-B*4001 Genotype and Stavudine-induced Lipodystrophy in HIV patients: A Systematic Review and Meta-analysis

Wimonchat Tangamornsuksan [1], Ornrat Lohitnavy [2] and Manupat Lohitnavy [3*]

[1,2,3] Center of Excellence for Environmental Health & Toxicology, Pharmacokinetic Research Unit, Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok, Thailand.

[*] Corresponding author. E-mail address: manupatl@gmail.com

Abstract

Objectives: This study aimed to systematically review and quantitatively synthesize an association between HLA genotype and stavudine-induced lipodystrophy in HIV patients.

Design: Systematic review and meta-analysis.

Methods: A systematic search for studies that investigated the association between HLA genotype and stavudine-induced lipodystrophy was performed in six databases (i.e. PubMed, Embase, CINAHL, IPA, HuGENet, and Cochrane Library). A meta-analysis was conducted to determine the association between specific HLA genotypes and stavudine-induced lipodystrophy by using a random-effects model. Quality assessments were performed using Downs and Black checklist. Potential sources of heterogeneity were examined.

Results: Two cross-sectional studies involving 439 HIV/AIDS patients who received stavudine-containing antiviral regimen (242 stavudine-induced lipodystrophy cases and 197 controls) were included. Only the prevalence of HLA-B*4001 genotype was investigated in both studies. We did not find any association between HLA-B*4001 and stavudine-induced lipodystrophy (overall OR = 3.13; 95% CI = 0.40-24.14) in a random-effects meta-analysis. A substantial heterogeneity was observed (I^2 = 79.4%, p = 0.027).

Conclusions: From our systematic review of a limited number of available studies, the association between HLA-B*4001 genotype and stavudine-induced lipodystrophy cannot be concluded. Ethnicity, duration of stavudine exposure, patient selection process and small sample size may contribute to the difference in results of the included studies. Future prospective studies with a larger sample size in Thai population and different ethnic groups are needed to verify the association between HLA-B*4001 genotype and stavudine-induced lipodystrophy.

Keywords: Human leukocyte antigen (HLA), lipodystrophy, stavudine, meta-analysis

Introduction

Stavudine is a nucleoside analogue reverse-transcriptase inhibitor used in combination with other anti-HIV drugs ("Stavudine approved under accelerated drug-approval process," 1994). At present, it is not recommended as a first-line drug for treatment of HIV infection due to its potential to cause disfiguring, painful and life threatening side-effects such as lipodystrophy, peripheral neuropathy and lactic acidosis (United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO), 2009. However, stavudine is still widely used in developing and underdeveloped countries due

to its efficacy and inexpensiveness (Smyth, et al., 2005, pp. 367-373; United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO), 2009). Stavudine continues to play a critical role in anti-retroviral therapy, stavudine was still contained in HIV regimens approximately 56% (World Health Organization, 2009). The main adverse effects of stavudine are symmetrical peripheral neuropathy (Domingo, et al., 2010; Van Griensven, et al., 2007, pp. 793-798) and lipodystrophy (Bharadwaj, et al., 2010, pp. 495-516; Chung, Too, Murad, & Hussein, 2007, pp. 221-224; Kim, Ye, Palikhe, Kim, & Park, 2010, pp. 280-290; Tozzi, 2010, 190-200). The prevalence of stavudine-induced lipodystrophy was 50-63% in western studies (Bernasconi, et al., 2002, pp. 50-55; Heath, et al., 2001, pp. 231-239; Saint-Marc, et al., 1999, pp. 1659-1667) whereas 17% in Thai population (Puttawong, Prasithsirikul, & Vadcharavivad, 2004, pp. 605-611). These suggested that genetic of ethnicity might affect stavudine-induced lipodystrophy (Subbaraman, Chaguturu, Mayer, Flanigan, & Kumarasamy, 2007, pp. 1093-1101).

Recently, the role of genetic factors, particularly human leukocyte antigen (HLA) polymorphism, in adverse drug reactions (ADR) has been implicated in several studies (Bharadwaj, Illing, & Kostenko, 2010, pp. 495-516). HLA is a set of genes that encode major histocompatibility complex (MHC), a group of proteins that have potential roles in the immune system Bharadwaj, Illing, & Kostenko, 2010, pp. 495-516; Chung, Hung, & Chen, 2007, pp. 317-323). The relationships between certain HLA genotypes and the risk of some ADRs have been established (Chang, Too, Murad, & Hussein, 2011, pp. 221-224; Chantarangsu, et al., 2009, pp. 139-146; Mallal, et al., 2002, pp. 727-732; Somkrua, Eickman, Saokaew, Lohitnavy, &

Chaiyakunapruk, 2011.), for example, polymorphic HLA genotypes are commonly associated with ADR (e.g. allopurinol and carbamazepine) (Chang, et al., 2011, pp. 221-224; Chantarangsu, et al., 2009, pp. 139-146; Mallal, et al., 2002, pp. 727-732; Somkrua, et al., 2011; Tangamornsuksan, Chaiyakunapruk, Somkrua, Lohitnavy, & Tassaneeyakul, 2013, pp. 1025-1032). For some anti-HIV agents, abacavir and nevirapine are more likely to produce more ADR among patients who possess HLA-B*5701 (Berka, Gill, Liacini, O'Bryan, & Khan, 2012, pp. 164-167; Mallal, et al., 2002, pp. 727-732) and HLA-B*3505 / HLA-Cw*4101 (Chantarangsu, et al., 2009, pp. 139-146; Likanonsakul, et al., 2009, pp. 142-150), respectively.

For stavudine, the association between HLA genotype and stavudine-induced lipodystrophy in HIV patients was documented (Domingo, et al., 2013; Wangsomboonsiri, et al., 2010, pp. 597-604). However, results of these previous studies remained inconsistent among difference of ethnicity and magnitude of the association. Major limitations of the individual observational studies are relatively small sample size and insufficient power. Thus, we conducted a systematic review and a quantitative evaluation of the association between HLA genotype and stavudine-induced lipodystrophy in HIV patients, based on data from observational studies.

Methods

Data sources and search strategy

A systematic literature search in PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), International Pharmaceutical Abstracts (IPA), Human Genome Epidemiology Network (HuGENet) and Cochrane Library, was performed from inception until January 2014. The combinations of keywords or synonyms

for "HLA genotypes" and "stavudine" were used for searching. There was no restriction on language or study design. Only human studies were included. Additional relevant studies were retrieved from references listed in the selected articles.

Study selection

Two reviewers (Wimonchat, & Ornrat) independently screened the titles and/or abstracts and then the full-text articles retrieved from the comprehensive searches for inclusion. Studies were included if (1) the association between the HLA genotype and stavudine-induced adverse drug reaction was investigated; (2) all patients in both cases and control groups received stavudine before the HLA genotype screening, and; (3) sufficient data for calculating frequency of carriers of the HLA genotype among both cases and control groups were reported.

Data extraction and quality assessment

The relevant information from all of the selected articles was independently extracted by two reviewers (Wimonchat, & Ornrat) which included study design, eligibility criteria, definition and diagnostic criteria for the cases and controls, patient demographics, dose and duration of stavudine exposure, and the HLA genotyping technique. The genotype frequencies of specific HLA genotype were calculated to determine whether the included populations were in Hardy-Weinberg equilibrium (HWE). HWE implies that the included individuals are likely to be representative of the population (Mayo, 2008, pp. 249-256; Salanti, Sanderson, & Higgins, 2005, pp. 13-20). Any disagreements on study inclusion and data extraction were discussed until a consensus was made between both reviewers.

Downs and Black checklist, a tool developed for evaluating the quality of randomized and non-randomized studies, was employed to assess the quality of the included studies (Downs, & Black, 1998, pp. 377-384). This checklist consists of 5

quality domains (27 items) [reporting (n=10), external validity (n=3), internal validity bias (n=7), internal validity confounding (n=6), and power (n=1)].

Data analysis

The overall ORs with corresponding 95% confidence intervals (95% CIs) were calculated to determine the association between the presence of a specific HLA allele and a stavudine-induced lipodystrophy. All analyses were performed using a random-effects model described by DerSimonian and Laird (DerSimonian, & Laird, 1986, pp. 177-188). Statistical heterogeneity was assessed via the Q-statistic and I-squared tests (Higgins, & Thompson, 2002, pp. 1539-1558). A p-value of $\leq$ 0.10 indicated heterogeneity between the included studies. I-squared values of 25%, 50%, 75% denoted a low, moderate, and high level of heterogeneity across studies, respectively (Higgins, Thompson, Deeks, & Altman, 2003, pp. 557-560). All statistical analyses were performed using the STATA software version 11.0 (StataCorp, College Station, TX, USA).

Result

Study selection

Our literature search and study selection process are summarized in Figure 1. The initial search from databases identified 1,955 articles. After the duplicate records were removed, 1,681 articles were first screened on the basis of title and/or abstract to determine the eligibility. Subsequently, a total of 220 full-text articles were screened and a further 218 were excluded because (1) they were review articles or case reports (89 records); (2) they were not human studies or not relevant (i.e. validated methods (30 records); (3) the patients in the studies did not receive stavudine (15 records), and (4) the studies did not investigate the association between HLA genotype and stavudine-releated adverse drug

reactions (84 records). Finally, two studies (Domingo, et al., 2013; Wangsomboonsiri, et al., 2010, pp. 597-604) met the inclusion criteria and

were included in the final review. No additional articles were identified in the bibliographies of the included studies.
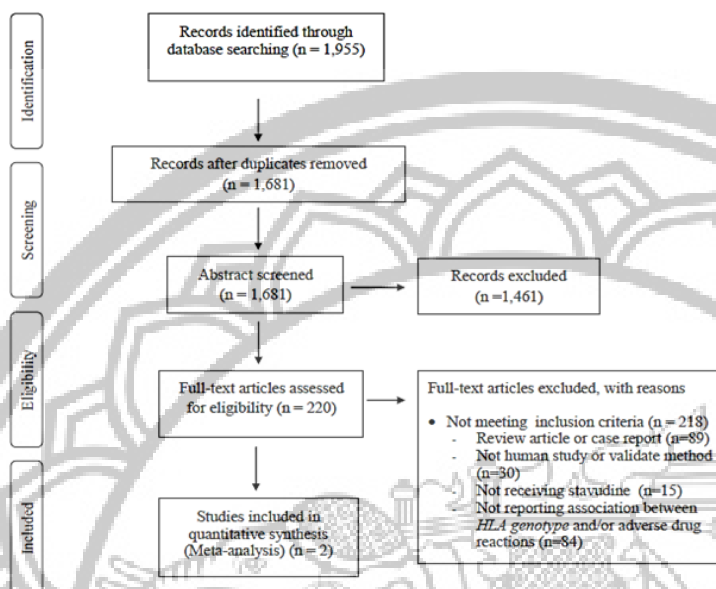

Figure 1 Literature search and study selection processes

Study characteristics

Characteristics of the included studies are summarized in Table 1 and 2. All of the studies investigated the association between HLA-B*4001 genotype and stavudine-induced lipodystrophy. Both studies were cross-sectional studies conducted in two different populations, i.e., Southeast Asian (Thai) (n = 103) (Wangsomboonsiri, et al., 2010, pp. 597-604) and Caucasian (Spanish) (n = 336). (Domingo, et al., 2013) The studies involved a total of 439 HIV/AID patients; 242 cases of stavudine-induced lipodystrophy and 197 patients in the control group, with the mean ages of 42.9 and 42.5 years, respectively. Men comprised 68.6% of the cases (166/242) and 70.0% of controls (138/197). The dose of stavudine in both studies was 30 mg or 40 mg twice daily based on the body weight (Chantarangsu, et al., 2009, pp. 139-146; Domingo, et al., 2013; Kiertiburanakul, et al., 2008, pp. 65-69).

In Wangsomboonsiri, et al. (2010, pp. 597-604) study, all patients who had been exposed and continue to use stavudine at the time of lipodystrophy diagnosis were invited from the previous case-control studies (Chantarangsu, et al., 2009, pp. 139-146; Kiertiburanakul, et al., 2008, pp. 65-69) to participate in this study. The median duration of stavudine treatment was 47.8 and 44.8 months in cases and controls, respectively. For Domingo, et al. (2013) study, the controls were matched by the duration of stavudine exposure (± 6 months). However, the duration of stavudine use and time after stopping stavudine were not reported. Only 75 out of 336 patients used stavudine at the time of study.

In both studies, lipodystrophy was independently assessed by patient self-evaluation and physical examination with a lipodystrophy severity grading scale (Carr, et al., 2003, pp. 571-576; Lichtenstein, et al., 2001, pp. 1389-1398). In brief, any lipoatrophy and diffused fat accumulation

at each of the following region: face, neck, dorsocervical spine, arms, breasts, abdomen, buttocks, and legs, was recorded and rated as absent (score of 0), mild (noticeable on a close inspection; score of 1), moderate (readily noticeable by a patient and/ or a physician; score of 2) or severe (readily noticeable to a casual observer; score of 3). The diagnostic criteria for lipodystrophy in both studies were slightly different but still based on the severity, number and affected area of the body. Cases were defined as patients with "moderate to severe lipodystrophy" whereas the patients whose signs were too mild or no sign of lipodystophy were identified as controls.

The polymerase chain reaction (PCR) technique and sequence-based typing were used to identify HLA-B*4001. Both studies did not report information on HWE.

The quality assessment of Wangsomboonsiri, et al. (2010, pp. 597-604) and Domingo et al. (2013) study by Downs and Black checklist were 17 and 16, respectively(Table 1). The items that were not reported and/or were incomplete involved selection process, follow-up process, blinding, and compliance.

Table 1 Characteristics of studies meeting the selection criteria.

Study [reference]	Study design	Nationality	Case		Control		Downs and Black checklist
			Positive	Negative	Positive	Negative	
Wangsomboonsiri, et al., 2010, pp. 597-604	Cross-sectional study	Thai	16	39	2	46	17
Domingo, et al., 2013	Cross-sectional study	Spanish	9	178	6	143	16

Table 2 Summary patient demographic information for the meta-analysis.

Parameter	Wangsomboonsiri, et al. , pp. 597-604			Domingo, et al.		
	Case (n=55)	Control (n=48)	P	Case (n=187)	Control (n=149)	P
A. Clinical characteristics						
Male (%)	29 (52.7)	20 (41.7)	0.262	137 (73.3)	118 (79.1)	0.249
Mean age, year (range)	41.9	41.1	0.585	44 (40.0-51.7)	44 (41.0-49.0)	0.817
Start Dose, mg/day (range)	NR	NR	NR	NR	NR	NR
Mean Dose, mg/day (range)	NR	NR	NR	NR	NR	NR
Median Duration of stavudine Exposure (months)	47.8 (31.0-67.0)	44.8 (25.9-58.4)	0.161	NR	NR	NR

Table 2 (Cont.)

Parameter	Wangsomboonsiri, et al. , pp. 597-604			Domingo, et al.		
	Case (n=55)	Control (n=48)	P	Case (n=187)	Control (n=149)	P
B. Metabolic and fat characteristics						
Height (cm)	162.8	161.4	0.343	NR	NR	NR
Body weight at ART initiation (kg)	53.2	56.8	0.94	66.5 (58.0-73.0)	70.0 (61.5-75.0)	0.229
BMI at ART initiation (kg/m^2)	20.2	23.1	0.16	23.4	23.4	0.9218
Waist circumference	76.7	82.8	0.01	87.0	88.0	0.8412
Total fat (kg)	11.6	17.0	<0.001	12.0	14.1	<0.001
Total fat (%)	21.4	28.0	<0.001	8.1	22.5	<0.001
C. Laboratory characteristics						
FBS level (mg/dL)	95.0	95.0	0.992	97.2	93.6	0.022
Triglyceride level (mg/dL)	223.9	169.0	0.092	169.9	144.2	0.017
Total cholesterol level (mg/dL)	217.7	215.1	0.781	212.7	191.4	0.367
HDL cholesterol leve (mg/dL)	46.2	50.8	0.134	42.2	45.6	0.005
LDL cholesterol level (mg/dL)	122.1	132.1	0.247	120.6	107.1	<0.001

NR=not reported

Quantitative synthesis

Only one HLA genotype (HLA-B*4001) was extracted from the included studies to investigate its association with lipodystrophy induced by stavudine in HIV/AIDS patients. In the meta-analysis, overall frequencies of HLA-B*4001 allele were 10.3% (25 of 242) in the cases and 4.1% (8/197) in the control group. The overall OR for the association of HLA-B*4001 allele with the risk for stavudine-induced lipodystrophy was 3.13 (95% CI = 0.40-24.14) (Figure 2). The heterogeneity was substantial, indicating the significant variation between both studies (I^2 = 79.4%, p = 0.027). Therefore it cannot be concluded that the presence of HLA-B*4001 has association to the risk of lipodystrophy in patients who received stavudine.
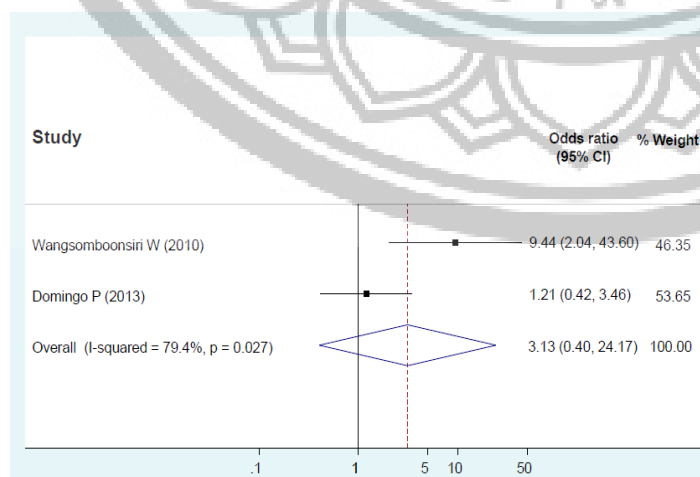

Figure 2 Random-effects meta-analyses of stavudine-induced lipodystrophy among HLA-B*4001 positive

Discussion

The objective of this study was to explore whether any specific HLA alleles were associated with stavudine-induced lipodystrophy. We analyzed two studies investigating the association between HLA-B*4001 alleles and lipodystrophy in patients who received stavudine. So far, HLA-B*4001 is the only HLA allele reported this association and only two studies provide sufficient data to conduct meta-analysis. The first study conducted in Thai population by Wangsomboonsiri, et al. (2010, pp. 597-604). demonstrated a significant positive correlation between HLA-B*4001 allele and stavudine-induced lipodystrophy However there was no significant association was observed in the study conducted in Spanish population by Domingo, et al. (2013).

The result from our meta-analysis cannot draw the conclusion due to substantial heterogeneity between both studies. To explore the potential sources of heterogeneity, we cannot conduct subgroup analysis due to a limited number of included studies. However, from our systematic review, the difference in results of Wangsomboonsiri et al. and Domingo et al. studies may be related to ethnicity, duration of stavudine exposure, and patient selection process.

Variability in HLA allele frequencies has been found in different populations. The frequency of HLA-B*4001 in Thai population is 0.055-0.085, which is much higher than that in Spanish population (0.025-0.05) (Allele Frequency Net Database, 2005). Since the numbers of the available studies of HLA genotype and stavudine-induced lipodystrophy were limited and the sample sizes were relatively small, the power might be too low to detect a difference in the distribution of HLA-B*4001 even though a true difference exists. More studies should be further conducted to confirm this association,

particularly in Asian populations (e.g. Han-Chinese, Malaysian, Korean and Japanese).

Lipodystrophy is a delayed adverse effect induced by stavudine. Incidence rate lipodystrophy after one year receiving stavudine was 14.7%. Incidence rates per 100 person-years during the second year receiving stavudine was 11.4 (Joep J. van, et al., 2012). Risk of lipodystrophy in HIV patients who received stavudine $\leq$ 2 years was about 26 fold-increased and about 15 fold-increased in $\geq$ 2 years user when compared with those whose did not received (Sang, et al., 2012). Nevertheless, after switching stavudine to abacavir, patients with moderate-to-severe lipodystrophy significant improvements in subcutaneous fat continued over 104 weeks (Martin, et al., 2004, pp. 1029-1036). These factors should be appropriately controlled as well as other factors such as concurrent drug use. Previous studies also demonstrated the association between other genes and lipodystrophy in certain populations, for example, Fas - 670AA genotype and APOC3 (Bonnet, et al., 2008, pp. 169-171; Likanonsakul, et al., 2013). There might be a complex interplay between several genes that involves the development of stavudine-induced lipodystrophy rather than a single HLA allele.

The selection of patients is another contributing factor that may cause the heterogeneity. There is a selection bias in Wangsomboonsiri et al. (2010, pp. 597-604) study since the patients were selected from a group of patients in previous case-control studies. Only the patients who maintained stavudine use were eligible which, in fact, a number of individuals who had been exposed to stavudine and changed to other regimens may still have lipodystrophy. Moreover, HWE should be tested and reported to check whether or not the included individuals were in equilibrium for the frequencies of genotypes (Mayo, 2008, pp. 249-256; Salanti,

et al., 2005, pp. 13-20). Equilibrium suggested that the included individuals are likely to be representative of the population (Smits, et al., 2005 pp. 13-20; Thakkinstian, McElduff, D'Este, Duffy, & Attia, 2005, pp. 1291-1306).

Lipodystrophy can be mediated through tumor necrosis factor α (TNF-α) and its signal transduction (Saint-Marc, et al., 1999, pp.1659-1667; Subbaraman, et al., 2007, pp. 1093-1101). However, the mechanism by which HLA-B*4001 contributed to stavudine-induced lipodystrophy is not well understood. Nonetheless, elevated TNF-α level were observed in HIV positive patients with stavudine-induced lipodystrophy (Christeff, Melchior, De Truchis, Perronne, & Gougeon, 2002, pp. 43-50). Thus, this cytokine might be responsible for lipodystrophy among these HIV patients.

Our meta-analysis has several limitations. Firstly, up to present, there are only two studies available in the literature, the association was observed in only two ethnicities (Thai and Spanish). Secondly, from these two studies, total sample size, was limited (242 cases and 197 controls). Thirdly, the diagnostic criteria for selected cases and control were different between the two studies. Thus, future prospective studies with a larger sample size in Thai population and different ethnic groups are needed to verify the association between HLA-B*4001 and stavudine-induced lipodystrophy.

Conclusions

From our systematic review of a limited number of available studies, the association between HLA-B*4001 and stavudine-induced lipodystrophy cannot be concluded. Future prospective studies with a larger sample size in Thai population and different ethnic groups are needed to verify the association between HLA-B*4001 and stavudine-induced lipodystrophy.

References

Allele Frequency Net Database. (2005). Allele frequencies in worldwide populations. Retrieved March 25, 2014, from http://www.allelefrequencies.net

Berka, N., Gill, J. M., Liacini, A., O'Bryan, T., & Khan, F. M. (2012). Human leukocyte antigen (HLA) and pharmacogenetics: screening for HLA-B*57:01 among human immunodeficiency virus-positive patients from southern Alberta. *Hum Immunol, 73*(2), 164-167.

Bernasconi, E., Boubaker, K., Junghans, C., Flepp, M., Furrer, H., Haensel, A., et al. (2002). Abnormalities of body fat distribution in HIV-infected persons treated with antiretroviral drugs: the Swiss HIV cohort study. *J Acquir Immune Defic Syndr, 31*(1), 50-55.

Bharadwaj, M., Illing, P., & Kostenko, L. (2010). Personalized medicine for HLA-associated drug-hypersensitivity reactions. *Personalized Medicine, 7*(5), 495-516.

Bonnet, E., Bernard, J., Fauvel, J., Massip, P., Ruidavets, J., & Perret, B. (2008). Association of APOC3 polymorphisms with both dyslipidemia and lipoatrophy in HAART-receiving patients. *AIDS Res Hum Retroviruses, 24*(2), 169-171.

Carr, A., Law, M., & Group., H. L. C. D. S. (2003). An objective lipodystrophy severity grading scale derived from the lipodystrophy case definition score. *J Acquir Immune Defic Syndr, 33*(5), 571-576.

Chang, C.-C., Too, C., Murad, S., & Hussein, S. (2011). Association of HLA-B*1502 allele with carbamazepine-induced toxic epidermal necrolysis and Stevens-Johnson syndrome in the multi-ethnic Malaysian population. *Int J Dermatol, 50*(2), 221-224.

Chantarangsu, S., Mushiroda, T., Mahasirimongkol, S., Kiertiburanakul, S., Sungkanuparph, S., Manosuthi, W., et al. (2009). HLA-B*3505 allele is a strong predictor for nevirapine-induced skin adverse drug reactions in HIV-infected Thai patients. *Pharmacogenet Genomics, 19*(2), 139-146.

Christeff, N., Melchior, J., De Truchis, P., Perronne, C., & Gougeon, M. (2002). Increased serum interferon alpha in HIV-1 associated lipodystrophy syndrome. *Eur J Clin Invest., 32*(1), 43-50.

Chung, W., Hung, S., & Chen, Y. (2007). Human leukocyte antigens and drug hypersensitivity. *Current Opinion in Allergy & Clinical Immunology, 7*(4), 317-323.

DerSimonian, R., & Laird, N. (1986). Meta-analysis in clinical trials. *Control Clin Trials, 7*(3), 177-188.

Domingo, P., Cabeza, M., Pruvost, A., Salazar, J., Gutierrez Mdel, M., Mateo, M., et al. (2010). Relationship between HIV/Highly active antiretroviral therapy (HAART)-associated lipodystrophy syndrome and stavudine-triphosphate intracellular levels in patients with stavudine-based antiretroviral regimens. *Clin Infect Dis, 50*(7), 1033-1040.

Domingo, P., Mateo, M., Pruvost, A., Torres, F., Salazar, J., Gutierrez, M., et al. (2013). Polymorphisms of Pyrimidine Pathway Enzymes Encoding Genes and HLA-B*40:01 Carriage in Stavudine-Associated Lipodystrophy in HIV-Infected Patients. *PLoS One, 8*(6), e67035.

Downs, S., & Black, N. (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomized and non-randomized studies of health care interventions. *J Epidemiol Community Health, 52*(6), 377-384.

Heath, K., Hogg, R., Chan, K., Harris, M., Montessori, V., O'Shaughnessy, M., et al. (2001). Lipodystrophy-associated morphological, cholesterol and triglyceride abnormalities in a population-based HIV/AIDS treatment database. *AIDS, 15*(2), 231-239.

Higgins, J., & Thompson, S. (2002). Quantifying heterogeneity in a meta-analysis. *Stat Med, 21*(11), 1539-1558.

Higgins, J., Thompson, S., Deeks, J., & Altman, D. (2003). Measuring inconsistency in meta-analyses. *BMJ, 327*(7414), 557-560.

Joep J. van, O., Jane, M., Symon, K., Newton, C., Yassin, N., Elizabeth, K., et al. (2012). Stavudine Toxicity in Adult Longer-Term ART Patients in Blantyre, Malawi. *PLoS One, 7*(7), e42029.

Kiertiburanakul, S., Sungkanuparph, S., Charoenyingwattana, A., Mahasirimongkol, S., Sura, T., & Chantratita, W. (2008). Risk factors for nevirapine-associated rash among HIV-infected patients with low CD4 cell counts in resource-limited settings. *Curr HIV Res, 6*(1), 65-69.

Kim, S., Ye, Y., Palikhe, N. S., Kim, J., & Park, H. (2010). Genetic and ethnic risk factors associated with drug hypersensitivity. *Current Opinion in Allergy & Clinical Immunology, 10*(4), 280-290.

Lichtenstein, K., Ward, D., Moorman, A., Delaney, K., Young, B., Palella, F. J., et al. (2001). Clinical assessment of HIV-associated lipodystrophy in an ambulatory population. *AIDS., 15*(11), 1389-1398.

Likanonsakul, S., Rattanatham, T., Feangvad, S., Uttayamakul, S., Prasithsirikul, W., Srisopha, S., et al. (2013). Polymorphisms in Fas gene is associated with HIV-related lipoatrophy in Thai patients. *AIDS Res Hum Retroviruses, 29*(1), 142-150.

Likanonsakul, S., Rattanatham, T., Feangvad, S., Uttayamakul, S., Prasithsirikul, W., Tunthanathip, P., et al. (2009). HLA-Cw*04 allele associated with nevirapine-induced rash in HIV-infected Thai patients. *AIDS Res Ther, 6*(22), 139-146.

Mallal, S., Nolan, D., Witt, C., Masel, G., Martin, A. M., Moore, C., et al. (2002). Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet, 359*(9308), 727-732.

Martin, A., Smith, D., Carr, A., Ringland, C., Amin, J., Emery, S., et al. (2004). Reversibility of lipoatrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir: the MITOX Extension Study. *AIDS, 18*(7), 1029-1036.

Mayo, O. (2008). A century of Hardy-Weinberg equilibrium. *Twin Res Hum Genet, 11*(3), 249-256.

Puttawong, S., Prasithsirikul, W., & Vadcharavivad, S. (2004). Prevalence of lipodystrophy in Thai-HIV infected patients. *J Med Assoc Thai, 87*(6), 605-611.

Saint-Marc, T., Partisani, M., Poizot-Martin, I., Bruno, F., Rouviere, O., Lang, J., et al. (1999). A syndrome of peripheral fat wasting (lipodystrophy) in patients receiving long-term nucleoside analogue therapy. *AIDS, 13*(13), 1659-1667.

Salanti, G., Sanderson, S., & Higgins, J. (2005). Obstacles and opportunities in meta-analysis of genetic association studies. *Genet Med, 7*(1), 13-20.

Sang, H. H., Jialun, Z., Suneeta, S., Sasheela, V., Nittaya, P., Yi-Ming A, C., et al. (2012). Prevalence of and risk factors for lipodystrophy among HIV-infected patients receiving combined antiretroviral treatment in the Asia-Pacific region: results from the TREAT Asia HIV Observational Database (TAHOD). *Endocr J. PMC, 58*(6), 475-484.

Smits, K., Schouten, J., Smits, L., Stelma, F., Nelemans, P., & Prins, M. (2005). A review on the design and reporting of studies on drug-gene interaction. *J Clin Epidemiol, 58*(7), 651-654.

Smyth, K., Affandi, J., McArthur, J., Bowtell-Harris, C., Mijch, A., Watson, K., et al. (2005) Prevalence of and risk factors for HIV-associated neuropathy in Melbourne, Australia 1993-2006. *HIV Med, 8*(6), 367-373.

Somkrua, R., Eickman, E., Saokaew, S., Lohitnavy, M., & Chaiyakunapruk, N. (2011). Association of HLA-B*5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *BMC Med Genet,* 12, 118.

Stavudine approved under accelerated drug-approval process. (1994). *Am J Hosp Pharm, 51*(17), 2087.

Subbaraman, R., Chaguturu, S., Mayer, K., Flanigan, T., & Kumarasamy, N. (2007). Adverse effects of highly active antiretroviral therapy in developing countries. *Clin Infect Dis, 45*(8), 1093-1101.

Tangamornsuksan, W., Chaiyakunapruk, N., Somkrua, R., Lohitnavy, M., & Tassaneeyakul, W. (2013). Relationship Between the HLA-B*1502 Allele and Carbamazepine-Induced Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Systematic Review and Meta-analysis. *JAMA Dermatol, 149*(9), 1025-1032.

Thakkinstian, A., McElduff, P., D'Este, C., Duffy, D., & Attia, J. (2005). A method formeta-analysis of molecular association studies. *Stat Med, 24*(9), 1291-1306.

Tozzi, V. (2010). Pharmacogenetics of antiretrovirals. *Antiviral Research, 85*(1), 190-200.

United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO). (2009). AIDS epidemic update. Retrieved March 25, 2014., from http://www. unaids.org/en/media/unaids/ contentassets/dataimport/pub/report/2009/jc1700_e pi_update_2009_en.pdf

Van Griensven, J., De Naeyer, L., Mushi, T., Ubarijoro, S., Gashumba, D., Gazille, C., et al. (2007). High prevalence of lipoatrophy among patients on stavudine-containing first-line antiretroviral therapy regimens in Rwanda. *Trans R Soc Trop Med Hyg, 101*(8), 793-798.

Wangsomboonsiri, W., Mahasirimongkol, S., Chantarangsu, S., Kiertiburanakul, S., Charoenyingwattana, A., Komindr, S., et al. (2010). Association between HLA-B*4001 and lipodystrophy among HIV-infected patients from Thailand who received a stavudine-containing antiretroviral regimen. *Clin Infect Dis. , 50*(4), 597-604.

World Health Organization. (2009). WHO Rapid Advice. *Antiretroviral therapy for HIV infection in adults and adolescents.* Retrieved March 25, 2014., from http://www. who.int/hiv/pub/arv/rapid_advice _art.pdf