CLINICALLY SIGNIFICANT DRUG INTERACTIONS AMONG HIV-INFECTED PATIENTS RECEIVING ANTIRETROVIRAL THERAPY

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Abstract. We conducted a cross sectional study of the outpatient medical records of 1,000 HIV-infected patients receiving antiretroviral therapy (ART) in 2011 to determine the incidence of clinically significant drug interactions (CSDI). The severities of the CSDI were graded following the Micromedex® 2.0 database and the Department of Health and Human Services (DHHS) 2012 HIV treatment guidelines. Three hundred thirty-five patients (34%) had 554 episodes of CSDI. Of which 337 episodes (61%), 163 episodes (29%) and 54 episodes (10%) had grades 2, 3 and 4 severity CSDI, respectively. The CSDI were caused by protease inhibitor (PI)-based drug regimens in 79%, by efavirenz-based regimens in 34% and by nevirapine-based regimens in 10% (p<0.001). The three most common grade 4 CSDI were: a PI with simvastatin (n=24), simvastatin with gemfibrozil (n=24) and didanosine with allopurinol (n=2). The three most common grade 3 CSDI were: a PI with a statin drug except simvastatin (n=56), fenofibrate with a statin drug (n=28) and amlodipine with simvastatin (n=14). On multivariate analysis, risk factors associated with CSDI were: receiving a PI-based regimen (OR 14.44; 95%CI: 9.10-22.88), having dyslipidemia (OR 3.94; 95%CI: 1.89-8.21), having >5 items prescribed at a time (OR 1.80; 95%CI: 1.23-2.63), seeing a doctor >4 times a year (OR 1.72; 95%CI: 1.20-2.46), having hypertension (OR 0.60; 95%CI: 0.37-0.98), having a duration of receiving ART of >5 years (OR 0.46; 95%CI: 0.28-0.77) and having a CD_4 count of >200 cells/mm^3 (OR 0.46; 95%CI: 0.26-0.84). CSDI were common among HIV-infected patients receiving ARV in our outpatient clinic. Patients having a low CD_4 count, having dyslipidemia, receiving PI-based ART, having a frequent number of visits per year and having a large number of items prescribed at each visit had a greater chance of a CSDI.

Keywords: antiretroviral, drug interaction, HIV, Thailand

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INTRODUCTION

High active antiretroviral therapy (HAART) therapy is effective in suppressing HIV replication and decreasing morbidity and mortality in treated patients (Palella *et al*, 1998; Ives *et al*, 2001). The

Department of Health and Human Services guideline (DHHS, 2012), the World Health Organization guideline (WHO, 2010), and the Thai national guideline (Sungkanuparph *et al*, 2010) all recommend three drug antiretroviral (ARV) regimens to treat HIV. In resource-rich countries, using 2 nucleoside reverse transcriptase inhibitors (NRTI) as backbone drugs combined with one of the following drug classes are preferred regimens: non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), or integrase inhibitors (DHHS, 2012). However, the choices may be limited in resource-constrained countries to only three drug classes: NRTI, NNRTI and PI (Sungkanuparph *et al*, 2010). Most current ARV drugs are associated with a higher risk for metabolic complications (Schambelan *et al*, 2002). Patients often require medications to treat co-morbid conditions. Several drugs used to treat these complications are metabolized by the cytochrome P450 (CYP450) system. Most current ARV drugs pass through the CYP450 pathway, thus HIV-infected patients receiving ARV drugs have the potential to have clinically significant drug interactions (CSDI) (Fichtenbaum and Gerber, 2002; Griffin *et al*, 2011). Based on the pharmacokinetic interactions, this may result in a decrease or increase in plasma levels of the drugs. Pharmacodynamic interactions may also increase or decrease adverse drug reactions. Therefore, CSDI are an important problem. CSDI in some patients receiving ART may be life-threatening or cause treatment failure (Cheng *et al*, 2002; Bongiovanni and Tordato, 2006). One study from a developed country (Miller *et al*, 2007) reported CSDI are common among patients receiving ARV drugs. Many risk factors have been described, such as having other comorbidities, older age or receiving PI-based ART regimens (Miller *et al*, 2007). Knowledge regarding the prevalence and risk factors for CSDI in a resource-limited setting is limited. In this study, we aimed to examine the prevalence, patterns of and risk factors for CSDI in the prescriptions of HIV-infected patients receiving antiretroviral therapy (ART) and attending an outpatient HIV clinic in a resource-limited setting.

MATERIALS AND METHODS

This cross sectional study was conducted at the HIV clinic, Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health, Nonthaburi, Thailand. This institute is a 300-bed tertiary HIV referral center located northwest of Bangkok. The protocol for this study was approved by the Ethics Committee for Research in Human Subjects, Department of Disease Control, Ministry of Public Health, Thailand and the institutional review board. Data were collected between January 1 and December 31, 2011. The outpatient medical records of 1,000 patients who had attended the clinic during the study period were randomly selected. Inclusion criteria were: 1) HIV-infected patients, 2) aged greater than 15 years, and 3) those receiving ARV drugs during the study period.

The data collected from the patient's medical records and an electronic database were: sex, age, type of ART, date of starting ART, duration of receiving ART, co-morbid conditions, plasma HIV RNA levels, CD_4 cell count, number of visits, and other drugs received. A co-morbid condition was defined as any chronic disease. Curative diseases, such as pneumonia, tuberculosis, or treatable opportunistic infections, were not considered as co-morbid conditions. Low dose ritonavir

Table 1
Criteria for classification severity of drug interactions.

Severity grade	Management for drug interactions	Example
1	No significant effect. Safe in combination. Use standard dose or no dosing adjustment. Clinical significance unknown or no data available. Normally titration for drugs.	Zidovudine *vs* lopinavir/ritonavir. Lamivudine *vs* co-trimoxazole. Enalapril *vs* ibuprofen.
2	Use with caution. Monitor safety or efficacy of specific drug. Monitor specific clinical or laboratory tests. Monitor drug levels. Take drug at different times. Dosage adjustment may be required.	Efavirenz *vs* simvastatin. Lopinavir/ritonavir *vs* gemfibrozil. Calcium *vs* levothyroxine.
3	Carefully titrate dose (start low, go slow) and/or close monitoring for safety/efficacy. Do not co-administer unless benefit outweighs risk. Avoid if possible and/or consider an alternative drug.	PI *vs* warfarin. PI *vs* clarithromycin. Gemfibrozil *vs* rosuvastatin.
4	Contraindicated. Do not co-administer. Concurrent use is not recommend.	Simvastatin *vs* gemfibrozil. PI *vs* simvastatin. Didanosine *vs* allopurinol.

used as a pharmacokinetic enhancing drug was not considered an active ARV drug. Any visit requiring hospitalization was not considered an outpatient visit.

Drug interactions were defined using two sources: 1) the 2012 Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, developed by the Department of Health and Human Services (DHHS, 2012) and 2) Micromedex® drug interaction software version 2.0 (Micromedex® Healthcare Series). Drug interactions were defined as: 1) pharmacokinetic drug interactions were those in which one drug interfered with the absorption, distribution, metabolism or excretion of another drug requiring a dosage adjustment to avoid an adverse drug reaction and/or maintain efficacy and 2) pharmacodynamic interactions were those in which both drugs were synergistic, additive or blocked the pharmacological effects of each other, requiring a change to avoid an adverse drug reaction or decreased efficacy.

Medications of the studied patients were entered into Micromedex® drug interaction software (Micromedex® Healthcare Series; Thomson Micromedex, Greenwood Village, CO). The software identified potential drug interactions and classified the interaction by degree of severity as follows: 1) contraindicated–concurrent use of the drugs was contraindicated, 2) major–a potentially life threatening interaction and/or an interaction requiring medical intervention to minimize or prevent serious adverse effects, 3) moderate–the interaction had the potential to cause an exacerbation of the patient's condition and/or require an alteration in therapy, 4) minor–the

Table 2
Baselines characteristics.

Characteristics	Number (%)
Age, years, mean ± SD	45.62 ± 8.28
Male	579 (57.9)
Number of antiretroviral drugs	
1	16 (1.6)
2	51 (5.1)
3	921 (92.1)
4	12 (1.2)
Antiretroviral drug regimens	
NVP-based regimens	485 (48.5)
EFV-based regimens	280 (28)
PI-based regimens	199 (19.9)
Other regimens	36 (3.6)
Duration of antiretroviral therapy, years, mean ± SD	8.4 ± 2.3
Comorbidities	
Number of comorbidities	
None (0)	546 (54.6)
1	259 (25.9)
2	149 (14.9)
3	45 (4.5)
4	1 (0.1)
Characteristic of co-morbid conditions	
Diabetes mellitus	114 (11.4)
Dyslipidemia	382 (38.2)
Hypertension	172 (17.2)
Others	28 (2.8)

interaction had the potential to limit the effectiveness of the therapy and increase the frequency or severity of the side effects but generally would not require a major alteration in therapy, 5) unknown. In our study, we did not consider unknown or minor interactions.

Medications of the studied patients were also checked using the 2012 Department of Health and Human Services guidelines for CSDI (DHHS, 2012). Drug interactions were then recorded and graded for severity (Table 1). If the severity was graded differently between the Micromedex® software and DHHS guidelines, we followed the DHHS guidelines. Although ritonavir was not considered as a primary HIV drug, CSDI between ritonavir and non-PI were included in the results.

Descriptive statistics were used to describe studied variables. Categorical variables were compared using the Pearson chi-square test. To identifying risk factors for CSDI, stepwise logistic regression analysis was used to control for possible confounding variables. Variables with a p-value <0.05 on univariate analysis were included on multivariate analysis. All p-values were 2-tailed, and a p-value <0.05 was considered statistically significant. SPSS for Windows (version 20 software package; IBM, Armonk, NY) was used for statistical analysis.

RESULTS

One thousand patients were included in the study. A summary of baseline characteristics is shown in Table 2. Ninety-two percent of patients were prescribed triple ARV drug regimens. Forty-eight point five percent were prescribed nevirapine (NVP)-based regimens, 28.0% were prescribed efavirenz (EFV)-based regimens, 19.9% were prescribed PI-based regimens and 3.6% were prescribed other regimens. Of the 36 patients who were prescribed other regimens, 28 (77.8%) received a prescription containing both PI and NNRTI drugs. Four hundred fifty-four patients (45.4%) had comorbidities. The three most common co-morbid conditions were dyslipidemia (38.2%), diabetes mellitus (11.4%) and hypertension (17.2%).

Of the 1,000 patients included in the study, CSDI were identified in 335 patients (33.5%). Ninety-six patients had at least one level of interaction. Prevalence of each CSDI for each regimen by severity

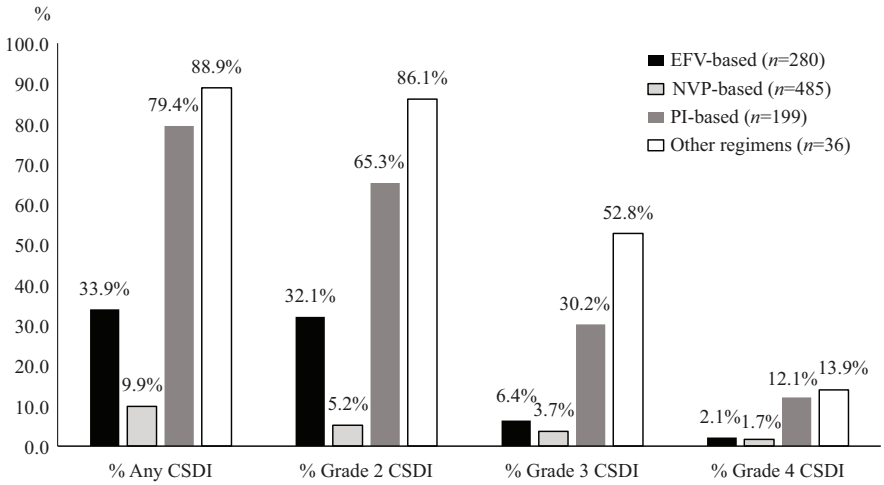

Fig 1–Prevalence of clinically significant drug interactions by regimen classified by severity grade. CSDI, clinically significant drug interactions; EFV-based, efavirenz-based regimens; NVP-based, nevirapine-based regimens; PI-based, protease inhibitors-based regimens. Any CSDI was defined as a regimen where at least one CSDI was found.

grade is shown in Fig 1. Among a total of 554 CSDI, 337(60.8%) were grade 2, 163 (29.4%) were grade 3, 54 (9.7%) were grade 4. The first five most common CSDI are shown in Table 3. The most common non-ARV drugs involved in CSDI were HMG Co-A reductase inhibitors, fibrates, dihydropyridine calcium channel blockers (DHP-CCBs), azoles, macrolides, divalent ion products, benzodiazepines and fluoroquinolones. PI and EFV were the most common ARV drugs involved in CSDI, especially interaction between tenofovir disoproxil fumarate (TDF) and PI.

When comparing CSDI by ARV regimen, the most common CSDI were found among patients receiving PI-based regimens. The possible risk factors associated with CSDI are shown in Table 4. On multivariate analysis, risk factors associated with CSDI were: receiving a PI-based regimen (OR 14.44; 95%CI: 9.10-22.88), having dyslipidemia (OR 3.94; 95%CI: 1.89-8.21), having >5 items prescribed at a time (OR 1.80; 95%CI: 1.23-2.63), seeing a doctor >4 times a year (OR 1.72; 95%CI: 1.20-2.46), having hypertension (OR 0.60; 95%CI: 0.37-0.98), having a duration of ART >5 years (OR 0.46; 95%CI: 0.28-0.77) and having a CD_4 count of >200 cells/mm^3 (OR 0.46; 95%CI: 0.26-0.84).

DISCUSSION

CSDI among ARV treated HIV-infected patients were common (33.5%). A previous study found a prevalence of 41.2% (Miller *et al*, 2007). The higher prevalence of CSDI in their study could be explained by the greater proportion of patients with PI-based regimen in their study (58.8%) than in our study (19.9%). PI are mainly metabolized via cytochrome P450 enzymes present in the liver and small intestine. Many drugs used concurrently to treat common comorbid conditions are metabolized by the same pathway; thus, PI may interact with these drugs. Sub-analysis revealed a high probability of CSDI among patients who received PI

Table 3
Characteristics of the five most frequent clinically significant drug interactions.

Severity	Frequency	ARV *vs* ARV	ARV *vs* other	Other *vs* other
Grade 2	337 (61%)	TDF *vs* PI (80)	EFV *vs* statins (85)	Pioglitazone *vs* gemfibrozil (7)
		NNRTI *vs* PI (29)	LPV/r *vs* gemfibrozil (34)	Calcium or ferrous *vs* other drugs (7)
		DDI *vs* PI (19)	PI *vs* DHP CCBs (16)	Psylliumhusk *vs* other drugs (5)
		IDV *vs* LPV/r (1)	NVP *vs* azoles (7)	Clorazepate *vs* omeprazole (2)
			AZT *vs* pyrazinamide (4)	Simvastatin *vs* ciprofloxacin (2)
				Azithromycin *vs* simvastatin (2)
				Amoxicillin *vs* medroxyprogesterone (2)
				Simvastatin *vs* levothyroxine (2)
Grade 3	163 (29%)	LPV/r *vs* SQV (3)	PI *vs* statins (not simvastatin) (56)	Fenofibrate *vs* statin (28)
			ARV *vs* clarithromycin (10)	Amlodipine *vs* simvastatin (14)
			PI *vs* benzodiazepines (7)	Gemfibrozil *vs* statin (not simvastatin) (12)
			LPV/r *vs* fluconazole (5)	Amitriptyline *vs* norfloxacin (2)
			ARV *vs* medroxyprogesterone (5)	Clarithromycin *vs* rosuvastatin (2)
Grade 4	54 (10%)	NVP *vs* EFV (1)	PI *vs* simvastatin (24)	Simvastatin *vs* gemfibrozil (24)
			DDI *vs* allopurinol (2)	Itraconazole *vs* simvastatin (1)
			DRV/r *vs* salmeterol (1)	
			ATV/r *vs* salmeterol (1)	

TDF, tenofovirdisoproxilfumarate; PI, protease inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; DDI, didanosine; IDV, indinavir; LPV/r, lopinavir/ritonavir; EFV, efavirenz; statins, all drugs in HMG-CoA reductase inhibitors; statins (not simvastatin), all HMG-CoA reductase inhibitors except simvastatin; DHP CCBs, dihydropyridine calcium channel blockers; NVP, nevirapine; AZT, zidovudine; SQV, saquinavir; ARV, antiretroviral drugs; DRV/r, darunavir/ritonavir; ATV/r, atazanavir/ritonavir.

in our study, similar to previous studies (Miller *et al*, 2007; Katende-Kyenda *et al*, 2008; Yiu *et al*, 2011). PI have the potential to interact with some NRTI, especially TDF and didanosine. TDF is primarily secreted in the urine via multidrug resistance protein 2 (MRP2), found on the apical surface of proximal renal tubule

Table 4
Univariate and multivariate analyses of possible risk factors associated with clinically significant drug interactions.

Parameters	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Duration of ART >5 years	0.43 (0.29-0.62)	<0.001	0.46 (0.28-0.77)	0.003
Last CD_4 cell count > 200 cells/mm^3	0.49 (0.32-0.77)	0.001	0.46 (0.26-0.84)	0.011
Male sex	1.70 (1.30-2.23)	<0.001	1.07 (0.75-1.54)	0.704
Age >50 years	1.75 (1.30-2.36)	<0.001	1.40 (0.94-2.07)	0.100
Having hypertension as a co-morbid conditions	1.84 (1.32-2.58)	<0.001	0.60 (0.37-0.98)	0.043
Number of visits per year >4 visits	2.41 (1.84-3.15)	<0.001	1.72 (1.20-2.46)	0.003
Number of items per prescription >5 items	2.52 (1.92-3.30)	<0.001	1.80 (1.23-2.63)	0.002
Last viral loads ≥50 copies/ml	2.54 (1.57-4.10)	<0.001	1.29 (0.68-2.43)	0.434
Having diabetes mellitus as a co-morbid condition	3.29 (2.21-4.90)	<0.001	1.24 (0.71-2.15)	0.447
Having co-morbid conditions	4.50 (3.39-5.96)	<0.001	1.75 (0.77-3.96)	0.179
Having dyslipidemia as a co-morbid condition	4.92 (3.71-6.52)	<0.001	3.94 (1.89-8.21)	<0.001
Taking a PI-based regimen	14.12 (9.61-20.74)	<0.001	14.44 (9.1-22.88)	<0.001

cells. Ritonavir is a potent inhibitor of MRP2-mediated transport (Miller, 2001; Rodriguez-Novoa *et al*, 2009). Therefore, ritonavir can potentially increase proximal tubular concentrations of TDF. A previous study among Thais found a high rate of renal dysfunction among patients who concurrently received PI and TDF (Chaisiri *et al*, 2010). This is concerning since they are both preferred second-line ARV drugs, especially in resource-limited countries, where routine screening of renal function is lacking. Some interactions were not related to the CYP450 system or P-gp pathway, such as calcium, iron or psyllium husks versus other drugs. Some drug interactions are not well defined, such as pyrazinamide and zidovudine.

Grade 2 CSDI were the most common interactions in the present study. The most common drug class involved was lipid lowering agents. Dyslipidemia has been reported with long term use of NNRTI and PI (Schambelan *et al*, 2002; Haubrich *et al*, 2009). Regarding dyslipidemia management, HMG-CoA reductase inhibitors and fibrates are the drugs of choice. HMG-CoA reductase inhibitors are cleared through the cytochrome P450 system and P-gp pathway (Fichtenbaum and Gerber, 2002; Griffin *et al*, 2011). As a consequence, there is a greater risk of statin-associated drug toxicity. On logistic regression, we found a number of risk factors associated with CSDI, including duration of ART, CD4 cell count, number of visits per year, number of drugs prescribed, presence of dyslipidemia and hypertension as a co-morbid conditions and a PI-based treatment regimen. All these factors were associ-

ated with HIV treatment complications and advanced HIV disease itself. Patients with a CD4 cell count >200 cells/mm^3 had a lower risk of CSDI than those with a lower CD4 cell count. Major opportunistic infections are less likely to develop after immune reconstitution. Patients with more drugs prescribed or more visits per year had a higher risk of CSDI. The metabolic derangements, such as dyslipidemia and diabetes mellitus type 2, have been reported after receiving ART. HMG-CoA reductase inhibitors and fibrates, are used in these patients, resulting in a greater risk of CSDI.

The present study had a number of limitations. First, the study was not designed to investigate the clinical outcomes of the drug interactions. Second, the patient and medical data were retrieved from their medical records and an electronic database. Other sources of information were not investigated, such as interviewing the patient. Finally, this study did not consider the dosage of interacting drugs. Further investigations are needed and should include drug dosages. Further management is needed to minimize drug interactions and improve HIV services.

CSDI were highly prevalent among HIV-infected patients receiving ARV at an outpatient clinic in a resource-limited setting. Patients with a low CD4 cell count, who have dyslipidemia, who are receiving PI-based ART, who have frequent physician visits per year and who have a large number of drugs prescribed have a higher chance of a CSDI.

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