Prevalence of potential drug-drug interactions in HIV-infected adults taking antiretroviral drugs at Vajira Hospital

Kittisak Pholtawornkulchai MD[1]*
Sirote Luengsupabul MD[2]

[1] Division of Infectious Disease, Department of Medicine, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand
[2] Somdejprasangkharach XVII Hospital, Suphanburi, Thailand
* corresponding author, email address: kittisak@nmu.ac.th
Vajira Med J. 2019; 63(2) : 85-92
http://dx.doi.org/10.14456/vmj.2019.12

Abstract

Background: Patients with HIV who are receiving antiretroviral (ARV) therapy are at risk for drug interactions. Potential drug-drug interactions (PDDIs) are frequent. Data regarding potential drug-drug interactions in HIV-positive individuals in Thailand are limited.

Objectives: To investigate the prevalence and risk factors of PDDIs between ARVs and co-administered drugs.

Material and Method: A retrospective study of HIV patients treated at the infectious clinic of Vajira Hospital was performed from April 2014 to June 2014. PDDIs were screened by using the Liverpool drug interactions database, defined as red flag interaction (contraindicated, avoid, or not recommended), and orange flag interaction (caution, close monitoring, or capable of causing clinical deterioration).

Results: Of 1,320 patients, 711 (53.86%) were male and the mean age was 44 ± 9 years. Median CD4 count was 495 cells/mm^3 (11-1,657). Fourteen (1.06%) had tuberculosis coinfection. Overall 82.05% and 20.38% of patients received Non-nucleoside reverse-transcriptase inhibitors (NNRTI) and protease inhibitor (PI)-based regimens, respectively. Nevirapine is the most commonly used NNRTI (49.09%) while Lopinavir/ritonavir (LPV/r) is the most commonly used in PI (74.63%). A total of 533 patients out of 1,320 HIV patients (40.38%) were at risk for a PDDI. Red flag interactions were 1.81% (12/664 events) and orange flag interactions were 98.19% (652/664 events). Major interactions most frequently involved rifampicin in red flag interactions and statins in orange flag interactions. In the multivariate analysis, factors associated with having PDDIs were male gender (OR 1.30, 95% CI 1.01-1.68), advanced age (age ≥ 50 years) (OR 2.20, 95% CI 1.63-2.95), 2 co-medications (OR 13.56, 95% CI 8.53-21.55), ≥ 3 co-medications (OR 41.07, 95% CI 12.68-133.06), and tuberculosis coinfection (OR 44.02, 95% CI 2.62-739.47) respectively.

Conclusions: The prevalence of PDDIs is high among HIV-infected adults on ARV drugs at Vajira Hospital. The risk for PDDIs increased significantly in males, aged ≥ 50 years, with polypharmacy, and coinfection with tuberculosis.

Key words: HIV, antiretroviral drugs, drug-drug interaction

ความชุกของการใช้ยาที่มีแนวโน้มเกิดปฏิกิริยาต่อกันระหว่างยาต้านไวรัสเอชไอวีกับยาอื่นๆในผู้ป่วยติดเชื้อเอชไอวี ณ วชิรพยาบาล มหาวิทยาลัยนวมินทราธิราช

กิตติศักดิ์ ผลถาวรกุลชัย[1]*

ศิโรตม์ เหลืองศุภบูลย์ [2]

[1] หน่วยโรคติดเชื้อ ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์วชิรพยาบาล มหาวิทยาลัยนวมินทราธิราช กรุงเทพมหานคร ประเทศไทย

[2] กองอายุรกรรม โรงพยาบาลสมเด็จพระสังฆราช องค์ที่ 17, จังหวัดสุพรรณบุรี

* ผู้ติดต่อ, อีเมล: kittisak@nmu.ac.th

Vajira Med J. 2019; 63(2) : 85-92

http://dx.doi.org/10.14456/vmj.2019.12

บทคัดย่อ

ภูมิหลัง: ผู้ป่วยโรคติดเชื้อเอชไอวีที่ได้รับยาต้านไวรัสมีความเสี่ยงที่จะเกิดการใช้ยาที่มีแนวโน้มเกิดปฏิกิริยาต่อกันระหว่างยาต้านไวรัสเอชไอวีกับยาอื่นๆได้บ่อย ข้อมูลเกี่ยวกับความชุกการใช้ยาที่มีแนวโน้มเกิดปฏิกิริยาต่อกันระหว่างยาต้านไวรัสเอชไอวีกับยาอื่นๆในประเทศไทยมีจำกัด

วัตถุประสงค์: เพื่อศึกษาถึงความชุกและปัจจัยเสี่ยงที่มีผลต่อการใช้ยาที่มีแนวโน้มเกิดปฏิกิริยาต่อกันระหว่างยาต้านไวรัสเอชไอวีกับยาอื่นๆ

รูปแบบและวิธีดำเนินการวิจัย: เป็นการศึกษาแบบย้อนหลัง ผู้ป่วยติดเชื้อเอชไอวีที่ติดตามการรักษาที่แผนกโรคติดเชื้อโรงพยาบาลวชิรพยาบาล ช่วงเดือนเมษายนถึงมิถุนายน พ.ศ. 2557 เก็บข้อมูลการการใช้ยาที่มีแนวโน้มเกิดปฏิกิริยาต่อกันระหว่างยาต้านไวรัสเอชไอวีกับยาอื่นๆตาม Liverpool drug interaction database จำแนกเป็น red flag (ห้ามให้ร่วมกัน, ควรหลีกเลี่ยงหรือไม่แนะนำให้ใช้) และ orange flag (สามารถใช้ร่วมกันได้แต่ควรปรับลดขนาดหรือติดตามอย่างใกล้ชิด)

ผลการวิจัย: ผลการทบทวนผู้ป่วยจำนวน 1,320 คน มีเพศชาย 711 คน (ร้อยละ 53.86), อายุเฉลี่ย 44 ± 9 ปี, ค่าเฉลี่ย CD4 เท่ากับ 495 เซลล์/ลูกบาศก์เมตร (11-1,657), มีการติดเชื้อวัณโรคร่วม 14 คน (ร้อยละ 1.06) ยาต้านไวรัสที่ใช้ร้อยละ 20.38 เป็นกลุ่ม Protease inhibitors (PIs) ร้อยละ 82.05 เป็นกลุ่ม Non-nucleoside reverse transcriptase inhibitor (NNRTIs) โดยยาที่ใช้มากที่สุดในกลุ่ม NNRTIs คือยา nevirapine (ร้อยละ 49.09) ในขณะที่ lopinavir/ritonavir เป็นยาที่ใช้มากที่สุดในกลุ่ม PIs (ร้อยละ 74.63) พบความชุกของการใช้ยาที่มีแนวโน้มเกิดปฏิกิริยาต่อกันระหว่างยาต้านไวรัสเอชไอวีกับยาอื่นๆ ร้อยละ 40.38 (533/1320) จำแนกเป็นแบบ red flag interaction ร้อยละ1.81 (12/664) และแบบ orange flag ร้อยละ 98.19 (652/664) โดยยาที่พบว่ามีปฏิกิริยากับยาต้านไวรัสมากที่สุด คือ rifampicin ในกลุ่ม red flag และ statin ในกลุ่ม orange flag การวิเคราะห์ความแปรปรวนพหุคูณพบปัจจัยที่มีผลต่อการใช้ยาที่มีแนวโน้มเกิดปฏิกิริยาต่อกันระหว่างยาต้านไวรัสเอชไอวีกับยาอื่นๆคือ เพศชาย (OR 1.30, 95%CI 1.01-1.68), อายุมากกว่าหรือเท่ากับ 50 ปี (OR 2.20, 95%CI 1.63-2.95), การใช้ยาอื่นๆร่วมกับยาต้านไวรัสตั้งแต่ 2 ชนิด (OR 13.56, 95%CI 8.53-21.55), การใช้ยาอื่นๆร่วมกับยาต้านไวรัสตั้งแต่ 3 ชนิด (OR 41.07, 95%CI 12.68-133.06) และการติดเชื้อวัณโรคร่วมด้วย (OR 44.02, 95%CI 2.62-739.47)

สรุป: การใช้ยาที่มีแนวโน้มเกิดปฏิกิริยาต่อกันระหว่างยาต้านไวรัสเอชไอวีกับยาอื่นๆพบได้บ่อย ปัจจัยเสี่ยงที่สำคัญคือผู้ป่วยสูงอายุ เพศชาย การใช้ยาอื่นๆร่วมกับยาต้านไวรัสตั้งแต่ 2 ชนิดและ มีการติดเชื้อวัณโรคร่วมด้วย

Introduction

To date, about 1,175,084 people in Thailand have been infected with HIV; 431,475 Thai people are currently living with HIV. Approximately 8,535 people are diagnosed with HIV in Thailand each year. Of these, more than 300,000 cases have had treatment with antiretroviral drugs (ARVs).[1] According to current recommendations, all patients should be treated.

There are 4 groups of ARVs available in Thailand (Nucleoside reverse transcriptase inhibitors (NRTIs), Non-nucleoside reverse transcriptase inhibitors (NNRTIs), Protease inhibitors (PIs), and Integrase inhibitors). Based on Thai national guidelines for antiretroviral therapy in HIV-1 infected adults and adolescents 2010, Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens are recommended as preferred first-line treatment.

Because NNRTIs and PIs are metabolized in the liver via cytochrome P-450 they have a potential for drug-drug interaction which may be from drug transporter, glucuronidation enzyme, nuclear receptor activation and pH-dependent drug absorption.[2,3] The result of drug-drug interaction may affect treatment due to increased toxicity, decreased drug efficacy and worse outcomes like HIV drug resistance or virological failure.[1-4] Thus achieving treatment without drug-drug interaction is one of the challenges in controlling HIV infection.

The prevalence of drug-drug interaction has been reported to be 20-40% in developed countries but data from developing countries are lacking, including from Thailand.[3] We aimed to study the prevalence and risk factors of potential drug-drug interactions in HIV-infected adults taking antiretroviral drugs at Vajira Hospital.

Methods

Study population

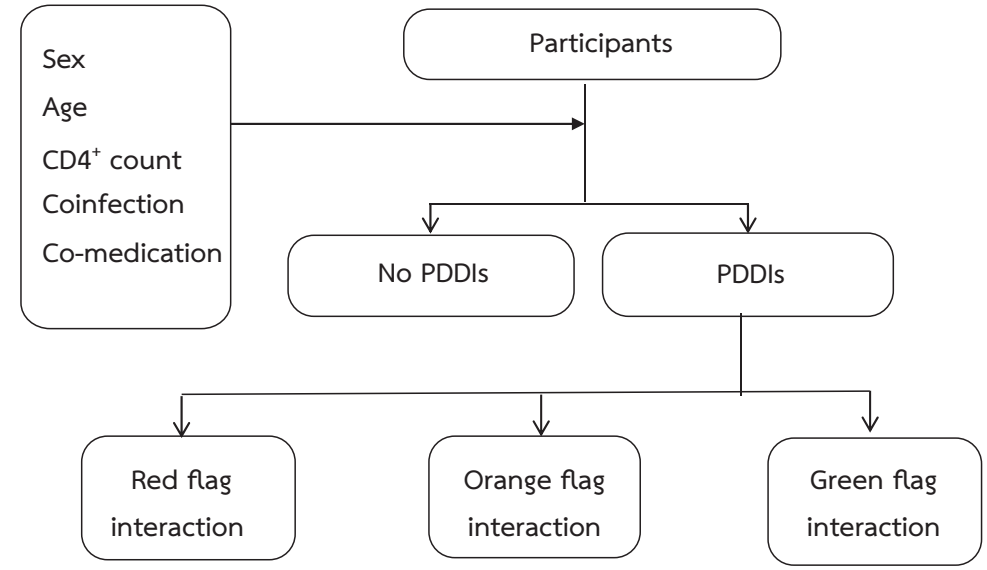
The study included patients from the HIV clinic of Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand. We enrolled all patients who were being treated with ARVs, aged ≥ 15 years. The data collection included baseline data, sex, age, CD4+ T cell count, type of ARVs, coinfection with HBV, HCV and tuberculosis, and concomitant drugs. The study was approved by local ethical review boards.

Study design

The data from all patients who attended HIV clinic from April 1, 2014 to June 30, 2014 were collected. To assess the risk of drug-drug interactions using the Thai national guidelines for antiretroviral therapy in HIV-1 infected adults and adolescents 2010, and the Liverpool drug interaction database,[5] patients were classified into three groups: a red flag for drugs that should not be used together due to possible severe adverse events, or impairment of the efficacy of ARVs; an orange flag indicates a potential interaction that may require dosage adjustment or close monitoring to minimize clinically adverse effects; and a green flag means no interaction.

Statistical analysis

Baseline characteristics, gender, age, CD4+ T cell count, ARV regimens, comedications, and coinfection were compared using Pearson's chi-square test. The prevalence of potential drug-drug interactions (PDDIs) is reported as a percentage. Multivariate logistic regression was used to investigate the factors associated with PDDIs, all odds ratios and their corresponding 95% confidence intervals were calculated. All the analyses were performed with the use of SPSS, version 22.0 for Windows.



*PDDI, Potential Drug-Drug Interaction

Figure 1: Study design

Results

Of the 1,320 patients included, 711 (53.86%) were male and mean age was 44 ± 9 years. Mean CD4 count was 495 cells/mm^3 (11-1,657). Overall 79.6% and 20.4% of patients received NNRTI and PI-based regimens, respectively. Nevirapine is the most commonly used NNRTI (62%), while Lopinavir/ritonavir (LPV/r) is the most commonly used PI (74%). Co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) was found in 9.62% (127/1320) and 7.58% (100/1320), respectively. Of all, 14 (1.06%) had tuberculosis coinfection and mainly rifampicin-containing regimen (12/14, 0.91%). More than half of these (56.06%, 740/1320) had co-administered another drug, 37.50% (495/1320) had at least 1 drug, 13.79% (182/1320) had at least 2 drugs and 4.70% (62/1320) had 3 or more used drugs with their ARVs. Baseline characteristics are shown in Table 1.

Overall, 40.38% (533/1320) had a potential drug-drug interaction: 1 PDDI in 59.1% (315/533), 2 PDDIs in 29.83% (159/533), and 3 or more in 11.1% (59/533). Patient characteristics, according to the presence of a potential drug-drug interaction, are shown in Table 1. Red-flag and orange flag interactions were found in 1.81% (12/664) and 98.19% (652/664) of the patients with comedication, respectively (Table 2). Most red flag interactions were nevirapine and rifampicin (0.75%, 5/664), while NNRTIs and statins accounted for most drug-drug interactions in the orange flag group (51.96%, 345/664).

According to univariate analysis, factors associated with potential drug-drug interactions were: male gender, age 50 years or more, coadministration of NNRTIs and PIs, coinfection with tuberculosis and ≥ 2 comedications. **(Table 1.)** The multivariate analysis showed that male gender (OR 1.30 [1.01-1.68]), age 50 years or more (OR 2.20 [1.63-2.95]), coinfection with tuberculosis (OR 44.02 [2.62-739.47]), 2 comedications (OR 1.25 [0.99-1.57]) and ≥ 3 comedications (OR 41.07 [12.68-133.06]) were associated with potential drug-drug interactions.

Table 1:

Baseline characteristics of the 1,320 patients according to the presence of a potential drug-drug interaction

Characteristic	Drug interaction (*n*=533)	No interaction (*n*= 787)	*P*-valvue
Age ≥ 50 years, *n* (%)	186 (34.90)	128 (16.26)	< 0.001
Male gender, *n* (%)	318 (59.66)	393 (49.94)	< 0.001
$CD4^+$ T-cell count, cells/mm^3			
≤ 50	11 (2.06)	10 (1.27)	0.023
51 – 200	47 (8.81)	47 (5.97)	0.052
201 - 350	88 (16.51)	141 (17.92)	0.482
> 350	387 (72.60)	589 (74.84)	0.264
Drug class			
PI, *n* (%)	114 (21.39)	154 (19.57)	0.413
NNRTI, *n* (%)	443 (83.11)	628 (79.80)	0.12
PI and NNRTI, *n* (%)	24 (4.50)	20 (2.54)	< 0.001
Tuberculosis coinfection, *n* (%)	14 (2.63)	0 (0.0)	< 0.001
HBV coinfection, n (%)	42 (7.88)	85 (10.80)	0.06
HCV coinfection, n (%)	41 (7.69)	59 (7.50)	0.89
Comedication			
≤ 1	315 (59.10)	762 (96.82)	< 0.001
2	159 (29.83)	23 (2.92)	< 0.001
3	59 (11.07)	3 (0.38)	< 0.001

PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor

Discussion

Drug-drug interaction is a common problem in general practice. In our cohort, the incidence of PDDI was 40.35%, which is high when compared with previously reports from the Netherlands, United States, United Kingdom, Switzerland and Kenya that estimated about 14-41%.[2,3,6] One percent were classified as red flag interactions, and 49% as orange flag interactions. Most PDDIs were due to rifampicin when concomitantly used with ART;[3] rifampicin is a potent inducer of cytochrome P450 CYP3A4, which affects the metabolism of antiretroviral drugs, including efavirenz, nevirapine and, the protease inhibitors. Higher doses of efavirenz are needed when it is used with rifampicin; and there is a question as to whether nevirapine is safe, given the risk of hepatotoxicity. While the used of PIs with rifampicin is a red flag interaction, concentrations of protease inhibitors are markedly decreased (>90%) compromising HIV treatment efficacy.[7,8]

Statins, which are commonly used for treating dyslipidemia in HIV-infected patients,[9] accounted for drug interactions with both NNRTIs (EFV and NVP) and PIs, especially red flag interactions between simvastatin and PIs, which may increase the risk of myopathy and rhabdomyolysis.[9] Thus, prescribers should be cautious and should use those medications with fewer interactions, such as atorvastatin or rosuvastatin [8-12]

Table 2:

Description of potential drug-drug interactions

Interaction	Drug 1	Drug 2	Description of the interaction	*n*
Red-flag interactions	Atazanavir	Omeprazole	Omeprazole decreased atazanavir AUC by 75**%**	1
	Nevirapine	Rifampicin	decreased nevirapine concentrations	5
	Nevirapine	Itraconazole	Itraconazole mean AUC and Cmax were significantly reduced by 61% and 38% respectively	2
	Lopinavir	Rifampicin	Large decreases in lopinavir concentrations	1
	Lopinavir	Simvastatin	simvastatin plasma concentrations are expected to increase markedly	2
	Efavirenz	Midazolam	could potentially decrease midazolam exposure	1
Orange-flag reactions	NNRTI/PI	Statins	decreased statin Cmax and AUC	345
	PI	Fibrates	decreased fibrates	37
	NNRTI/PI	CCB	predicted to increase CCB exposure	141
	NNRTI/PI	Anticonvulsants	increased or decreased anticonvulsants and/or efavirenz concentrations, decreased NVP concentration	6
	NNRTI/PI	Steroid	increased or decreased steroid concentrations	20
	NNRTI/PI	Antipsychotics	increased or decreased antipsychotic concentrations	46
	NNRTI/PI	Hormones	decreases hormone exposure	7
	EFV	Rifampicin	decreased EFV Cmax and AUC	6
	EFV/NVP	Colchicine	may reduce colchicine concentrations	3
	EFV/NVP	Azoles	may increase or decrease concentrations of azole	33
	NNRTI/PI	Warfarin	may increase or decrease warfarin concentrations	3
	NNRTI/PI	Clarithromycin	decreased clarithromycin Cmax , AUC and Cmin	2
	PI	Clopidrogel	decreased exposure of the active metabolite leading to non-responsiveness to clopidogrel	2
	PI	Omeprazole	Decreased omeprazole AUC	1

AUC, area under the curve; Cmax, maximum concentration; CCB, calcium channel blocker

Table 3:

Multivariate analysis of factors associated with potential drug interactions in patients treated with ARV and comedication

Characteristic	OR (95% CI)
Male gender	1.30 (1.01-1.68)
Age ≥ 50 year	2.20 (1.63-2.95)
PI and NNRTI	1.25 (0.99-1.57)
Comedication	
2	13.56 (8.53-21.55)
≥ 3	41.07 (12.68-133.06)
Tuberculosis coinfection	44.02 (2.62-739.47)

The risk factors that were associated with PDDIs included polypharmacy, consistent with previous studies.[2,3,6] Generally, those with more advanced age tended to have underlying disease including cardiovascular disease and dyslipidemia, and more potential to be treated with drugs that may affect ART. In this study, PDDI was more common among those aged 50 years or, and especially with concomitant use of ART and antihyperlipid drugs and antihypertensive drugs.[10,13-15] Information technology is a valuable tool in many hospitals to help physicians to recognize drug-drug interactions, such as alert systems but were ignored by physicians up to 55% - 91.2% of the time.[2,6]

Some limitations of the study included: 1) the incidence may be lower than the fact because some over the counter drug that had drug-drug interaction e.g. ergotamine were not included due to retrospective data collection; 2) the actual level of the drugs and clinical of the patient due to the change of drugs level are not evaluated but based on the reference data these data represented the pitfall and magnitude of the problem that may be used for developing the safety system for the clinician who cares the high risks group of the patients. [6,9,16-17]

Conclusions

The prevalence of PDDIs is high among HIV-infected adults on ARV drugs at Vajira Hospital. The risk for PDDIs increased significantly in males, aged ≥ 50 years, with polypharmacy, and coinfection with tuberculosis.

Part of this work was presented at the 30th International Congress of Chemotherapy and Infection 2017 (ICC 2017), Abstract PS 534 Kittisak Pholtawornkulchai1, Sirote Luengsupabul. Prevalence of potential drug-drug interactions in HIV-infected adult on antiretroviral drugs at Faculty of medicine Vajira hospital, Navamindhradhiraj university

No funding or financial support was received for this work. The authors declare that they have no conflicts of interest in this work.

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