Frequency and Severity of Potential Drug Interactions in a Cohort of HIV-infected Patients Identified through a Multidisciplinary Team

E. Molas,¹ S. Luque,² A. Retamero,² D. Echeverría-Esnaol,² A. Guelar,¹ M. Montero,¹ R. Guerri,¹ L. Sorli,¹ E. Lerma,¹ J. Villar,¹ H. Knobel¹

¹Infectious Diseases Department, Hospital del Mar, Barcelona, Spain; ²Pharmacy Department Hospital del Mar, Barcelona, Spain. Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain

Keywords: HIV; Drug-drug interactions; Highly active antiretroviral therapy

Abstract

OBJECTIVES: Interactions between antiretroviral treatment (ART) and comedications are a concern in HIV-infected patients. This study aimed to determine the frequency and severity of potential drug-drug interactions (PDDIs) with ART in our setting.

METHODS: Observational study by a multidisciplinary team in 1259 consecutive HIV patients (March 2015-September 2016). Data on demographics, toxic habits, comorbidities, and current ART were collected. A structured questionnaire recorded concomitant medications (including occasional and over-the-counter drugs). PDDIs were classified into 4 categories: 1) no interactions, 2) mild (clinically nonsignificant), 3) moderate (requiring close monitoring or drug modification/dose adjustment), and 4) severe (contraindicated). Statistical analysis: chi-square test, logistic regression analysis.

RESULTS: In total, 881 (70%) patients took comedication, and 563 (44.7%) had $\geq$ PDDI. Forty-one comedicated patients (4.6%) had severe and 522 (59.2%) moderate PDDIs. Moderate PDDIs mainly involved cardiovascular (53.8%) and central nervous system (40.2%) drugs. Independent risk factors for PDDIs were ART containing a boosted protease inhibitor (odds ratio [OR]=9.11, 95% confidence interval [CI] 5.15-16.11; $p=0.0001$) and/or non-nucleoside reverse transcriptase (NNRTI) (OR=4.34, 95%CI 2.49-7.55; $p=0.0001$), HCV co-infection (OR=3.26, 95%CI 2.15-4.93; $p=0.0001$), and use of 2 or more comedications (OR=3.36, 95%CI 2.27-4.97; $p=0.0001$). Adherence and effectiveness of ART were similar in patients with and without PDDIs. The team made 133 recommendations related to comedications (drug change or dose adjustment) or ART (drug switch or change in administration schedule).

CONCLUSIONS: Systematic evaluation detected a significant percentage of PDDIs requiring an intervention in HIV patients on ART. Monitoring and advice about drug-drug interactions should be part of routine practice.

Introduction

Recent advances in antiretroviral therapy (ART) have led to reductions in disease progression and improved survival in patients with human immunodeficiency virus (HIV) infection (1). The increased life expectancy in this population has converted HIV into a chronic disease, and a large percentage of patients are older than 50 years (2). This implies that increasingly more patients have comorbidities (both age- and HIV disease-related) and a greater need for various drug treatments (3) (4) (5).

In previous studies investigating the prevalence of potential drug-drug interactions (PDDIs) in several geographic regions, the rate of clinically relevant interactions between antiretrovirals and concomitant drugs is reported at 14% to 41% (6) (7) (8) (9) (10) (11). PDDIs can be associated with higher toxicity and lower effectiveness of both antiretrovirals and the comedications. Because of the inherent characteristics of antiretroviral drugs, many of which are enzyme inducers or inhibitors, PDDIs are common in HIV patients (12).

Numerous articles, including some epidemiologic studies and reviews, have focused on pharmacokinetic interactions between different drugs (13) (14) (15). Furthermore, excellent information sources contain recommendations for managing these interactions according to their severity. Nonetheless, epidemiologic studies on this subject and analyses of the clinical recommendations carried out are limited in large HIV cohorts (16).

The primary aim of this study was to determine the prevalence and clinical relevance of the main PDDIs occurring in our setting, with a focus on the impact of a multidisciplinary team intervention used to manage this problem. Additional objectives were to analyze the most frequent antiretroviral drugs and comedications implicated in PDDIs, evaluate the risk factors for PDDIs, and determine the impact of these interactions on the effectiveness of ART.

Material and methods

Patients

Cross-sectional observational study including all HIV patients aged 18 years and older followed in Hospital del Mar (Barcelona, Spain) between March 2015 and March 2016.

Information on epidemiologic and sociodemographic factors, comorbidities, and the ART and comedications received was collected through a personal interview with each patient and by consulting the hospital Pharmacy Department's electronic database for antiretroviral drug dispensing and the electronic prescriptions in the patient's medical records. A structured questionnaire was used to compile information on all concomitant medications patients were taking: regular and occasional prescription drugs, over-the-counter drugs, recreational drugs, phytotherapy, and alternative medicine products. In addition, at the time of the structured interview, data were recorded on CD4 lymphocyte count, plasma viremia, and adherence to ART (determined by a specific questionnaire for this purpose and the Pharmacy drug-dispensing registry).

Identification and classification of drug-drug interactions

PDDIs between ART and comedications were evaluated using the University of Liverpool HIV Drug Interaction Checker (www.hiv-druginteractions.org) (17). Information on interactions with drugs that were not included in this resource was retrieved from the Hospital Clínico database (Barcelona) (<http://www.interaccionesvih.com/html/interacciones.html>) and the Toronto General Hospital database (<http://hivclinic.ca/drug-information/drug-interaction-tables/>), or the existence of a PDDI was deduced based on the metabolic pathways of the implicated drugs. The potential interactions detected were classified according to their severity into four categories: 1) no interaction (known or predicted), 2) mild interaction (clinically nonsignificant); 3) moderate interaction (clinical monitoring of effectiveness or adverse effects, or potential dose adjustment required), and 4) severe interaction (contraindicated). In the analysis of the results, patients were divided into those without potential interactions (patients in the first two categories) and those with potential interactions (patients in the second two categories).

PDDIs were evaluated by a multidisciplinary team including 3 clinical pharmacists specialized in HIV from the hospital Pharmacy Department and 2 specialists from the Infectious Diseases Department. Following this assessment, a specific recommendation was reported to the attending physician by e-mail or immediate telephone contact in the case of severe PDDIs. We investigated the degree to which the proposed recommendations were accepted, evaluating the clinician's response to potential interactions considered severe and recording the changes made.

In the descriptive analysis, the chi-square test was used to compare proportions and the Mann-Whitney *U* test to compare quantitative variables. Multivariate regression analysis was performed to identify independent risk factors for the presence of moderate and severe PDDIs. Variables found to be significant ($p < .05$) in univariate analysis were added to the multivariate model. The study was approved by the hospital Ethics Committee, and all patients gave informed written consent to participate.

Results

Participants and characteristics of the medication

The study included 1259 patients from an overall cohort of approximately 1600 HIV-infected individuals. In total, 341 patients (23.1%) were excluded (Figure 1). The characteristics of the participants are summarized in Table 1. Most were Caucasian (81.2%) and men (80.3%), and the mean age was 47 years. The most common comorbidities were dyslipidemia (35.7%), psychiatric disorders (30.6%), and cardiovascular disease (14%).

Among the total, 70% (881/1259) were receiving comedications, and 44.7% (563/1259) had at least one clinically relevant PDDI. The potential interaction was classified as severe in 4.3% (41/881) and moderate in 59.2% (522/881) of patients taking comedications. A median of 2 concomitant drugs (IQR=1-16) were taken per patient in the overall cohort and a median of 3 drugs (IQR=2-5) in the PDDI group ($P<0.001$).

The characteristics of patients receiving comedications, presented according to whether or not a PDDI was detected are shown in Table 2. As the table expresses numbers of patients, and an individual patient could be exposed to different antiretroviral classes, the antiretroviral groups are mutually exclusive in this order: PI, NNRTI, INI, MVC, and NRTI.

The distribution of antiretrovirals used according to drug class was as follows: non-nucleoside reverse transcriptase inhibitors (NNRTIs), 663 (52.6%); nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), 633 (50.3%); ritonavir-boosted protease inhibitors (PI/r), 519/1259 (41.2%); integrase inhibitors (INI), 183 (14.5%); and CCR5 coreceptor inhibitors, 35 (2.7%).

Among patients receiving boosted PIs (519), the most common were darunavir (DRV/r; 60.3%), lopinavir (LPV/r; 19%), and atazanavir (ATV/r; 13.6%). The most frequent NRTI combinations were tenofovir (TDF) plus emtricitabine (FTC) (TDF+FTC; 306/633, 48.4%) and abacavir (ABC) plus lamivudine (3TC) (ABC+3TC; 295/633, 46.6%). The NNRTI most

often used was efavirenz (EFV; 240/663, 36%), followed by rilpivirine (RPV; 180, 27%), nevirapine (NVP; 163, 24.5%) and etravirine (ETV; 80, 12%).

In total, 379/1259 (30%) patients were taking triple ART combination regimens in a single tablet. The most common combinations were EFV/ABC/3TC (204; 16.2%) and RPV/FTC/TDF (152; 12.1%). PI/r monotherapy was used in 102/1259 (8%) patients. Eighty-four patients (6.6%) were taking dual therapy, the most common regimens being PI/r+INI (32; 38%), PI/r+NNRTIs (29; 34%), PI/r+NRTIs (12; 14.2%), PI/r+maraviroc (7; 8.3%), and NNRTIs+INI (4; 4.7%). Adherence to ART was >90% in most patients (1124/1259; 89.3%).

The antiviral classes associated with the most PDDIs were PI/r (254/519, 49%), with 219 (42%) moderate and 35 (7%) severe potential interactions. NNRTIs were next in frequency (210/660; 31.8%), with 204 (31%) moderate potential interactions and only 6 (1%) severe ones, followed by NRTIs (121/633, 19%), INI (22/183, 14.5%), and CCR5 coreceptor inhibitors (3/35, 8.5%).

The description of comedications by drug type, and the relationships between comedications and the presence and severity of PDDIs are described in Table 3. Prescription drugs, over-the-counter medications, and alternative medicine products are included. The most commonly prescribed therapies were cardiovascular and central nervous system (CNS) drugs, used in 53.8% and 40.2% of patients, respectively.

The recommendations proposed for patients with severe PDDIs and the concomitant drugs involved are summarized in Table 4.

Factors associated with the presence of potential drug-drug interactions in patients receiving antiretroviral therapy and comedications

The univariate and multivariate analyses of factors associated with PDDI detection in patients on ART are described in Table 5. After adjusting for demographic and HIV-related variables, the independent risk factors for the presence of PDDIs were hepatitis C virus (HCV) coinfection, ART regimen including a PI/r and/or NNRTI, and receiving ≥ 2 concomitant medications, with a significant increase in the risk of potential interactions when 4 or more concomitant drugs were used.

Recommendations for managing drug-drug interactions

The multidisciplinary team proposed 133 recommendations (23.6%; 133/563) for comedicated patients with PDDIs, and 91.7% (122/133) of the changes were accepted and carried out. The recommendations included a switch or dose adjustment of the concomitant treatment, or a switch or change in the timing of ART administration (Figure 1). Ninety-two (17.6%) changes were made for moderate PDDIs (n=522) and 30 changes (73.1%) for severe PDDIs (n=41). Recommendations for patients with severe PDDIs are described in Table 4. In most patients (23/41), the comedication was changed, mainly quetiapine, omeprazole, and simvastatin. The ART regimen was modified in only 7/41 patients, mainly by substituting the PI/r for another drug. Patients with severe PDDIs had undetectable viremia and a mean CD4+ T-lymphocyte count of 680.5 cells/ μ L ($\pm$ 375.2). Those with moderate PDDIs had a CD4+ count of 704.1 cells/ μ L ($\pm$ 299.3) ($p=0.220$).

No severe drug-related side effects occurred in any patient, including those with moderate or severe PDDIs. Most patients were asymptomatic, with the main symptom being somnolence in patients showing an interaction between quetiapine and the PI/r.

Discussion

Drug-drug interactions in patients receiving ART can affect the toxicity, drug resistance, and therapeutic levels of the treatment (18); hence, it is essential to identify potential interactions to achieve effective viral suppression and minimal toxicity. The overall PDDI detection rate in our large cohort of HIV-infected patients was 44.7%, with 3.2% corresponding to potentially severe interactions and the remainder to moderate interactions. The factors predictive of presenting a PDDI were related to the number of comedications used, HCV coinfection, and the ART regimen.

Coadministration of ART with other medications can result in significant changes in serum levels of the drugs, many of which are associated with preventable adverse effects (19). Most drug-drug interactions take place through an inducing or inhibitory effect on the CYP450 cytochrome system and/or P-glycoprotein, and some antiretroviral drug classes are associated with a higher risk of developing interactions. Ritonavir-boosted PIs are potent CYP3A4 inhibitors, and these drugs are the ones most commonly associated with drug-drug

interactions, including those producing severe reactions (20) (21) (22). The use of cobicistat as a PI booster or in combination with elvitegravir would have similar effects.

Most PDDIs seen in the present study were moderate interactions that would require monitoring to minimize clinical consequences. Severe PDDIs were detected in a small number of patients (41 patients, 3.2% of the total) and interventions were recommended (changes in ART or the comedication) in all cases, with acceptance of the recommendations in 73.2%. It should be mentioned that these percentages could show some variation because interactions are not uniformly categorized across all the guidelines. For example, quetiapine administered with PIs is contraindicated in the Liverpool guidelines, whereas it requires strict monitoring in in the FDA product insert (23) and Toronto database (24).

The review by Manzardo et al. (20) reported that severe interactions can have serious consequences and even endanger the patients' lives. Toxicity syndromes, cardiac arrhythmia, excessive sedation, severe hypotension, and Cushing's syndrome have been described in association with these interactions. Most of the clinically significant PDDIs detected in our analysis were related to the increasingly more common use of cardiovascular medication, opiates, CNS drugs (25) (26), and gastrointestinal medication.

Our results showed no difference in the adherence to ART or effectiveness of this treatment between patients with and without PDDIs, and there were no severe adverse events. One study has suggested that low rates of severe interactions result from medical care provided by expert specialists in HIV (16). In approximately one-quarter of our patients receiving concomitant medication, potential interactions were detected and a recommendation was needed beyond the usual clinical practice.

The limitations of this study, in addition to the variability in the classification of PDDIs, is that, as a single center study the findings are difficult to extrapolate to other health care settings, because of the type of patient included, the health professionals involved, and the antiretroviral drugs used. These factors can modify not only the percentage and severity of PDDIs, but also the need for monitoring and counseling.

The findings of the present study indicate that recording and assessing the medications (antiretrovirals and others) taken by HIV-infected patients is effectively achieved through the work of a multidisciplinary team (physicians experienced in HIV and specialized clinical pharmacists) to anticipate drug-drug interactions, improve the quality of the prescriptions, and guarantee patient safety.

Conflicts of interests

The authors declare that they have no conflicts of interest related to this article.

Table 1. Participant characteristics

Characteristics	Value
Total patients, n	1259
Patients with comedication, n	653
Patients with PDDIs, n	881
Age, y, median (SD)	47.38 (10.35)
Male, n (%)	1011 (80.3%)
Female, n (%)	248 (19.7%)
Race, n (%)	
Caucasian	1022 (81.2%)
Others	237 (18.8%)
Toxic habits, n (%)	
Smoking	669 (53.1%)
Current recreational drug use, n (%)	181 (14.4%)
Alcohol consumption	112 (8.9%)
HIV characteristics	
CD4 T-cell count, cells/μL, median (IQR)	650 (466-866)
Viral suppression <50 copies/mL, n (%)	1108 (88)
HCV coinfection, n (%)	382 (30.3%)
HBV coinfection, n (%)	68 (5.4%)
Comorbid conditions, n (%)	
Hyperlipidemia	450 (36.5%)
Psychiatric disorder*	386 (31.7%)
Cardiovascular disease**	177 (14%)
Gastrointestinal disease	98 (7.7%)

Diabetes mellitus	55 (4.3%)
Liver failure	41 (7.9%)
Kidney failure	45 (3.5%)
Respiratory disease	35 (2.7%)
Active neoplasm	23 (1.8%)
Others	196 (15.5%)

PDDIs, potential drug-drug interactions

*Includes high blood pressure, and ischemic and hypertensive heart disease

**Includes anxiety depressive syndrome, addiction, personality disorder, bipolar disorder, obsessive compulsive disorder, and schizophrenia

Table 2. Characteristics of the 881 HIV-infected individuals treated with antiretrovirals and comedications, according to the presence of a potential drug-drug interaction

Characteristics	Drug-drug interaction (n=563) 63.9%	No interaction (n=318) 36.1%	P-value
Age, y, (SD)	50 (10.7)	47 (9.6)	0.0001
Male, n (%)	444 (63.9)	251 (36.1)	1
Caucasian, n (%)	477 (65.6)	250 (34.4)	0.02
HCV coinfection, n (%)	240 (77.9)	68 (22.1)	0.0001
Median CD4 T-cell count, cells/μL, median (IQR)	631 (439-870)	697 (509-904)	0.1
Viral suppression <50 copies/mL, n (%)	491 (63.4)	283 (36.3)	0.4
Adherence ART >90%, n (%)	502 (63.8)	285 (36.2)	0.6
Comedication			
1 drug, n (%)	79 (32.3)	174 (67.7)	0.0001
2 drugs, n (%)	124 (61.4)	78 (38.6)	0.0001
3 drugs, n (%)	111 (76.6)	34 (23.4)	0.0001
≥ 4 drugs, n (%)	249 (88.6)	32 (11.4)	0.0001
Drug class			
PI, n (%)	302 (77)	90 (23)	0.0001
NNRTI, n (%)	248 (57.9)	180 (42.1)	0.0001

Table 3. Summary of drug-drug interactions between antiretrovirals and other drugs

INI, n (%)	90 (60)	60 (40)	0.3
------------	---------	---------	-----

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

Drug type	Nº patients receiving the drug	Nº patients with PDDIs	Nº patients with potential moderate interaction	Nº patients with potential severe interaction
Vitamins and minerals	313 (24.9%)	8 (6.4%)	8 (6.4%)	0
Vitamins	266 (21.1%)	7	7	0
Minerals	47 (3.7%)	1	1	0
Cardiovascular medications	677 (53.8%)	269 (21.4%)	262 (20.8%)	7 (0.6%)
Statins	227 (18.0%)	168	164	4
ACEIs	90 (7.1%)	2	2	0
Fibrates	81 (6.4%)	4	4	0
Antiplatelets and anticoagulants	69 (5.5%)	29	29	0
Beta blockers	60 (4.8%)	22	22	0
Diuretics	50 (4.0%)	3	2	1 (eplerenone)
ARBs	47 (3.7%)	11	11	0
Other antihypertensive agents	11 (0.9%)	5	5	0
Calcium antagonists	29 (2.3%)	20	20	0
Antianginal	9 (0.7%)	4	2	2 (ivabradine)
Antiarrhythmic	4 (0.3%)	1	1	0
Pain killers	175 (13.9%)	48 (3.8%)	48 (3.8%)	0 (0%)
Analgesics other than NSAIDs	84 (6.7%)	0	0	0

NSAIDs	65 (5.2%)	40	40	0
Morphine (without methadone)	26 (2.1%)	8	8	0
CNS medications	506 (40.2%)	255 (20.3%)	233 (18.5%)	22 (1.7%)
Anxiolytics, hypnotics and sedatives	192 (15.3%)	89	88	1 (midazolam)
Antidepressants	156 (12.4%)	100	99	1 (trazodone)
Anticonvulsants	82 (6.5%)	3	2	1 (phenytoin)
Antipsychotic and neuroleptic agents	76 (6.0%)	63	44	19
Gastrointestinal medications	185 (14.7%)	18 (1.4%)	10 (0.8%)	8 (0.6%)
PPIs	153 (12.2%)	8	0	8
H2 blockers	18 (1.4%)	8	8	0
Antacids	14 (1.1%)	2	2	0
Methadone	84 (6.7%)	70	70	0
Infectious Diseases medications	91 (7.2%)	29 (2.3%)	29 (2.3%)	0 (0%)
Antibiotics	69 (5.5%)	23	23	0
Antivirals	22 (1.7%)	6	6	0
Medicinal Plants	61 (4.8%)	10	10	0
Endocrine medications	107 (8.5%)	41 (3.3%)	41 (3.3%)	1 (0.1%)
Steroids	49 (3.9%)	21	21	1 (dexamethasone)
Antidiabetic drugs	48 (3.8%)	14	14	0
Bisphosphonates	10 (0.8%)	6	6	0
Respiratory medications				
Bronchodilators	58 (4.6%)	5	5	0
Others	155 (12.3%) Tamsulosin 18 Antigone 12 Levothyroxine1 1			
Immunosuppressants	6 (0.5%)			
Contraceptives	6 (0.5%)			

ACEIs; angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; NSAIDs, nonsteroidal anti-inflammatory drugs, PPIs, proton pump inhibitors

Table 4. Description of the severe potential drug-drug interactions in 41 patients

ARV involved	Drug other than ARV involved	Patients, n (%) (41)	Recommendations, n (%) (41)	
PI/r			Comedication change	ART change
PI/r	Quetiapine	19 (46.3%)	18 (94.7%)	1 (5.3%)
PI/r	Simvastatin	5 (12.2%)	5 (100%)	
ATV/r	Omeprazole	3 (7.3%)	1 (33.3%)	
PI/r	Ivabradine	2 (4.9%)		2 (100%)
PI/r	Midazolam	2 (4.9%)		2 (100%)
PI/r	Phenytoin	1 (2.4%)	1 (100%)	
SQV/r	Trazodone	1 (2.4%)	1 (100%)	
SQV/r	Eplerenone	1 (2.4%)	1 (100%)	
ATV/r	Nevirapine	1 (2.4%)		1 (100%)
NNRTIs				
RPV	Omeprazole	4 (9.8%)	3 (75%)	1 (25%)
NVP	Silodosin	1 (2.4%)	1 (100%)	
RPV	Dexamethasone	1 (2.4%)		1 (100%)

ARV, antiretroviral; PI/r, ritonavir-boosted protease inhibitor; ATZ/r, atazanavir/ritonavir; SQV/r, saquinavir/ritonavir; RPV, rilpivirine; NVP, nevirapine; NNRTIs, non-nucleoside reverse transcriptase inhibitors

Table 5. Factors associated with drug-drug interactions. Univariate and adjusted analysis of 881 HIV-infected patients receiving antiretroviral treatment and comedications

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Age x 10 years	1.41 (1.22-1.62)	0.0001	1.05 (0.88-1.25)	0.56
Caucasian	1.51 (1.06-2.15)	0.022	1.06 (0.68-1.64)	0.80
HCV coinfection	2.73 (1.99-3.75)	0.0001	1.93 (1.31-2.83)	0.001
ART drug class				
	Ref		Ref	
INI	4.99 (3.12-7.98)	0.0001	9.11 (5.15-16.11)	0.0001
PI	1.94 (1.23-3.05)	0.004	4.34 (2.49-7.55)	0.0001
NNRTI				
Comedication				
	Ref		Ref	
1 drug				
2 drugs	3.36 (2.27-4.97)	0.0001	3.26 (2.15-4.93)	0.0001
3 drugs	6.91 (4.32-11.04)	0.0001	6.95 (4.17-11.58)	0.0001
≥4 drugs	16.46 (10.43-25.97)	0.0001	19.36 (11.37-32.94)	0.0001

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

References

1. Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. 1998 Mar 26;338(13):853–60.
2. Marzolini C, Back D, Weber R, Furrer H, Cavassini M, Calmy A, et al. Ageing with HIV: medication use and risk for potential drug-drug interactions. *J Antimicrob Chemother*. 2011 Sep;66(9):2107–11.
3. Seden K, Merry C, Hewson R, Siccardi M, Lamorde M, Byakika-Kibwika P, et al. Prevalence and type of drug-drug interactions involving ART in patients attending a specialist HIV outpatient clinic in Kampala, Uganda. *J Antimicrob Chemother*. 2015 Dec;70(12):3317–22.
4. Effros RB, Fletcher CV, Gebo K, Halter JB, Hazzard WR, Horne FM, et al. Aging and infectious diseases: workshop on HIV infection and aging: what is known and future research directions. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2008 Aug 15;47(4):542–53.
5. Gleason LJ, Luque AE, Shah K. Polypharmacy in the HIV-infected older adult population. *Clin Interv Aging*. 2013;8:749–63.
6. Tseng A, Foisy M. Important Drug-Drug Interactions in HIV-Infected Persons on Antiretroviral Therapy: An Update on New Interactions Between HIV and Non-HIV Drugs. *Curr Infect Dis Rep*. 2012 Feb;14(1):67–82.
7. Miller CD, El-Kholi R, Faragon JJ, Lodise TP. Prevalence and risk factors for clinically significant drug interactions with antiretroviral therapy. *Pharmacotherapy*. 2007 Oct;27(10):1379–86.
8. Kigen G, Kimaiyo S, Nyandiko W, Faragher B, Sang E, Jakait B, et al. Prevalence of potential drug-drug interactions involving antiretroviral drugs in a large Kenyan cohort. *PLoS One*. 2011 Feb 23;6(2):e16800.
9. Evans-Jones JG, Cottle LE, Back DJ, Gibbons S, Beeching NJ, Carey PB, et al. Recognition of risk for clinically significant drug interactions among HIV-infected patients receiving antiretroviral therapy. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2010 May 15;50(10):1419–21.
10. Patel N, Abdelsayed S, Veve M, Miller CD. Predictors of clinically significant drug-drug interactions among patients treated with nonnucleoside reverse transcriptase inhibitor-, protease inhibitor-, and raltegravir-based antiretroviral regimens. *Ann Pharmacother*. 2011 Mar;45(3):317–24.

11. Iniesta-Navalón C, Franco-Miguel JJ, Gascón-Cánovas JJ, Rentero-Redondo L. Identification of potential clinically significant drug interactions in HIV-infected patients: a comprehensive therapeutic approach. *HIV Med.* 2015 May;16(5):273–9.
12. Serrano López de Las Hazas JL. Drug interactions of new antiretroviral drugs. *Farm Hosp Organo Of Expresion Cient Soc Espanola Farm Hosp.* 2011 Feb;35(1):36–43.
13. Vadlapatla RK, Patel M, Paturi DK, Pal D, Mitra AK. Clinically relevant drug-drug interactions between antiretrovirals and antifungals. *Expert Opin Drug Metab Toxicol.* 2014 Apr;10(4):561–80.
14. Berretta M, Caraglia M, Martellotta F, Zappavigna S, Lombardi A, Fierro C, et al. Drug-Drug Interactions Based on Pharmacogenetic Profile between Highly Active Antiretroviral Therapy and Antitlastic Chemotherapy in Cancer Patients with HIV Infection. *Front Pharmacol.* 2016;7:71.
15. Antoniou T, Tseng AL-I. Interactions between recreational drugs and antiretroviral agents. *Ann Pharmacother.* 2002 Oct;36(10):1598–613.
16. Marzolini C, Elzi L, Gibbons S, Weber R, Fux C, Furrer H, et al. Prevalence of comedications and effect of potential drug-drug interactions in the Swiss HIV Cohort Study. *Antivir Ther.* 2010;15(3):413–23.
17. Liverpool HIV Interactions [Internet]. [cited 2017 Mar 24]. Available from: <http://www.hiv-druginteractions.org/checker>
18. Foy M, Sperati CJ, Lucas GM, Estrella MM. Drug interactions and antiretroviral drug monitoring. *Curr HIV/AIDS Rep.* 2014 Sep;11(3):212–22.
19. Santos WMD, Secoli SR, Padoin SM de M. Potential drug interactions in patients given antiretroviral therapy. *Rev Lat Am Enfermagem.* 2016 Nov 21;24:e2832.
20. Manzardo C, Tuset M, Miró JM, Gatell JM. [Severe or life-threatening interactions between antiretrovirals and non-HIV drugs]. *Enferm Infecc Microbiol Clin.* 2015 Sep;33(7):e15-30.
21. Cervero M, Torres R, Jurdado JJ, Pastor S, Agud JL. [Predictive factors of clinically significant drug-drug interactions among regimens based on protease inhibitors, non-nucleoside reverse transcriptase inhibitors and raltegravir]. *Med Clin (Barc).* 2016 Apr 15;146(8):339–45.
22. Holtzman C, Armon C, Tedaldi E, Chmiel JS, Buchacz K, Wood K, et al. Polypharmacy and risk of antiretroviral drug interactions among the aging HIV-infected population. *J Gen Intern Med.* 2013 Oct;28(10):1302–10.
23. Research C for DE and. Postmarket Drug Safety Information for Patients and Providers - Kaletra (lopinavir/ritonavir) Information [Internet]. [cited 2017 Mar 24]. Available from: <https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm246021.htm>

24. Drug Interaction Tables | Immunodeficiency Clinic [Internet]. [cited 2017 Mar 24]. Available from: <http://hivclinic.ca/drug-information/drug-interaction-tables/>
25. Repetto MJ, Petitto JM. Psychopharmacology in HIV-infected patients. *Psychosom Med*. 2008 Jun;70(5):585–92.
26. Watkins CC, Pieper AA, Treisman GJ. Safety considerations in drug treatment of depression in HIV-positive patients: an updated review. *Drug Saf*. 2011 Aug 1;34(8):623–39.

Fig.1