



# Clinically significant drug interactions between antiretroviral and co-prescribed drugs in HIV infected patients: retrospective cohort study

Hawra Ali Hussain Al Sayed<sup>1</sup>, Narjes Saheb Sharif-Askari<sup>2</sup>,  
Mohammad Reza Rahimi<sup>3</sup>

1) Pharmacy Department, Rashid Hospital, Dubai Health Authority, Dubai, United Arab Emirates

2) Sharjah Institute of Medical Research, College of Medicine, University of Sharjah, Sharjah, United Arab Emirates

3) Medicine Department, Infectious Diseases Division, London Health Science Center, Ontario, Canada

## Abstract

**Introduction.** There are limited data on human immunodeficiency viruses (HIV) infected people in the UAE and the Gulf region. This study aimed at assessing the prevalence and risk factors for potential clinically significant drug interactions (CSDIs) in a cohort of 181 HIV infected people in Dubai.

**Methods.** A retrospective study was conducted at the outpatient infectious diseases clinic of Rashid hospital. Consecutive HIV seropositive people on anti-retroviral therapy (ART) were included. All potential CSDIs were analyzed and classified using Liverpool HIV drug interactions database.

**Results.** Nucleoside reverse transcriptase inhibitors (NRTIs) and integrase strand transfer inhibitors (INSTIs) were the most frequently used antiretroviral agents (ARVs), while the most common (non-ARV) were cardiovascular medication followed by antilipidemic statins. A total of 140 potential CSDIs were found in nearly half (n=86, 47.5%) of the 181 included HIV persons. Of the 140 potential CSDIs, 27 (19%) were of weak clinical relevance, 108 (77%) were of potential clinical relevance, and 5 (4%) were of contraindicated clinical relevance interactions. Moreover, 52 (37.14%) of CSDIs were between two ARVs and 88 (62.85%) were between ARV and non-ARV drugs. In the univariate analysis, age, dyslipidemia, number of medications, analgesics use, statin use, supplement intake, time since diagnosis of HIV, number of ART, and use of a protease inhibitor (PI) were significant. In the logistic regression, factors independently associated with CSDIs were the number of medications (odds ratio [OR] 1.165, 95% CI 1.021-1.329, P = 0.023) and the time since diagnosis of HIV (OR 1.156, 95% CI 1.008-1.327, P = 0.038).

**Conclusion.** The frequency of CSDIs between ART and co-medications is high in HIV seropositive people. Awareness of the risk factors may assist clinicians to recognize and manage CSDIs.

**Keywords:** clinically significant drug interaction (CSDI), Human Immunodeficiency Virus (HIV), antiretroviral therapy (ART), antiretroviral drug (ARV), risk factors

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Address for correspondence:

hawraa313ali@gmail.com

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## Introduction

Human Immunodeficiency Virus (HIV) infection is a continuum, where malignancies, infections, and other non-acquired immunodeficiency syndrome (AIDS) associated conditions are more frequent than in the general population. AIDS is the final stage of the disease, and treatment should attempt to avoid the development of this condition [1]. Significant advances related to HIV pathogenesis and viral replication have led to the development of many antiretroviral (ARV) drugs. Currently, the standard anti-retroviral regimen comprises a combination of at least three drugs targeting different stages of the HIV-1 viral replication cycle, the use of two-drug regimen dolutegravir plus lamivudine (DTG/3TC) approved for initial treatment in some cases [2].

Antiretroviral therapy (ART) is effective in suppressing the viral load and raising the blood levels of CD4<sup>+</sup> T lymphocytes reducing HIV-associated morbidity and mortality [3]. However, the efficacy of ART is directly linked to patient compliance and adherence, a lack of which could lead to the emergence of resistant strains which can be difficult to manage [4]. Drug interaction with potential adverse outcomes could hinder patient adherence to the ART treatment [5]. Hence, it is critical to anticipate any serious or clinically relevant drug-drug interactions (DDIs) that can affect ART treatment efficacy and safety [6].

The term clinically significant drug interaction (CSDI) indicates the likelihood of a particular medication changing the intensity of the pharmacological effects of another medication, therefore enhancing or minimizing the therapeutic effect and/or adverse reactions [7]. ART is considered one of the main therapeutic groups with the highest potential for DDI [8]. HIV protease, non-nucleoside reverse transcriptase inhibitors and certain integrase inhibitors undergo CYP mediated metabolism, and therefore, may interact with medications that are metabolized by this pathway [9]. These interactions could be life-threatening to patients, or they could lead to treatment failure for those receiving ARVs [10].

The incidence of drug interactions reported by previous investigations conducted in Europe and Africa ranged between 22% to 67%. This difference was attributed to the dissimilarity in sociodemographic as well as the clinical characteristics of the studied cohort such as variations in age, comorbidities, and medications [11,12]. Given the regional variation in patterns of interactions, there is an essential need to describe and assess this health problem among these persons from a Middle East country such as the United Arab Emirates (UAE). Therefore, this study was conducted to identify the frequency and characteristics of ARV associated potential CSDIs in Dubai, UAE.

## Methods

### Study design and population

A retrospective study was conducted at the outpatient infectious diseases clinic of Rashid hospital during a predefined 3-month period from 1 January to 31 March 2017. Ethical approval was obtained from the Dubai Scientific Research Ethics Committee (Reference No: DSREC-08/2017\_06), and all research in this study was performed in accordance with relevant guidelines and regulations. The informed consent was waived by the Dubai Scientific Research Ethics Committee. Rashid hospital is a tertiary specialized academic hospital that is part of the Dubai Health Authority. Consecutive HIV seropositive persons on ARVs attending the outpatient infectious diseases clinic aged 18 and above were included in the study.

### Data collection

We used a standardized data collection form for the purpose of this study. Patient data, including demographic data (age and gender), latest viral load, latest CD4 counts, date of HIV diagnosis, concurrent comorbid conditions, coinfection with hepatitis B or C viruses, and latent tuberculosis were collected from the medical records. Data on ARV prescription and all concomitant therapy which was prescribed by the same or different physician was recorded by reviewing the e-pharmacy system. Medications taken on as-needed basis were excluded from the count. Combination products were also counted as separate entities (e.g., zidovudine / lamivudine was counted as two agents). The following four main classes of ARVs were used by our patient: nucleoside reverse transcriptase inhibitors (NRTIs), integrase strand transfer inhibitors (INSTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs).

The medication list was gathered and entered into a predesigned data collection form. For the definition of potential CSDIs, we included all drug interactions between ARVs and non-ARVs. Interactions between non-ARVs were excluded. We screened and filtered the most common medications including antidepressants/antipsychotics, antihypertensives, statins, steroids, antiplatelets, analgesics, proton pump inhibitors (PPIs), calcium supplements, and multivitamins with minerals. The DDIs were screened and classified according to the Liverpool HIV drug interactions web-based resource ([www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)). This is a comprehensive database including more than 11,000 HIV DDIs which is extensively utilized throughout Europe and, since 2012, has involved all drugs from the WHO Model List of Essential Medicines. This database classified the clinical significance of each DDIs according to a traffic light system of red (contraindicated/do not co-administer), amber (potential interaction requiring dosage alteration/monitoring or timing of administration), yellow (weak clinical significance unlikely to require further management), or green (no clinically significant interaction) [13].

### Statistical analysis

Continuous variables were presented as the mean  $\pm$  standard deviation (SD) or median and interquartile range (IQR), if their distribution was skewed, and categorical variables were reported as counts and percentages. Student's t-test was used to compare the continuous data, and Chi-square test was performed for the categorical data [14]. Independent predictors of CSDIs were identified using a logistic regression analysis which was adjusted for age, sex, and any other variables that were significant in univariate analysis. All analyses were two-sided with a *P* value of 0.05 considered statistically significant. Analysis

was carried out using SPSS 26.00 (SPSS Inc., Chicago, IL, USA). Figures were generated using GraphPad Software 8.0, San Diego, Calif.

### Results

Of 190 HIV seropositive patient records screened, 181 patients were included in the analysis. We excluded nine patients that were not on antiretroviral therapy. Clinical characteristics, comorbidities, medications, HIV characteristics and antiretroviral medication of included patients are presented in table I.

**Table I.** Demographic and clinical characteristics of 181 HIV infected patients with and without clinically significant drug interactions (CSDIs).

Characteristics	Total (n=181)	CSDIs (n=86)	NO CSDI (n=95)	P-value
<b>Demographic</b>				
Age, years (Mean $\pm$ SD)	41 $\pm$ 12	43 $\pm$ 12	39 $\pm$ 11	0.022
Gender, n (%)				0.133
Male	132 (73 %)	58 (67 %)	74 (78 %)	
Female	49 (27 %)	28 (33 %)	21 (22 %)	
<b>Comorbidities</b>				
Psychiatric disorder, n (%)	12 (6)	8 (9)	4 (4)	0.169
Ischemic heart disease, n (%)	7 (4)	2 (2)	5 (5)	0.306
Diabetes mellitus, n (%)	25 (14)	11 (13)	14 (15)	0.705
Hypertension, n (%)	45 (25)	24 (28)	21 (22)	0.367
Dyslipidemia, n (%)	55 (30)	33 (38)	22 (23)	0.026
COPD/Asthma, n (%)	8 (4)	5 (6)	3 (3)	0.385
Cancer, n (%)	7 (4)	4 (5)	3 (3)	0.603
<b>Number of comorbidities, median (IQR)</b>	<b>1 (0-1)</b>	<b>1 (0-2)</b>	<b>1 (0-1)</b>	<b>0.05</b>
<b>Medications</b>				
Antidepressant/anxiolytics, n (%)	8 (4)	2 (2)	6 (6)	0.238
Cardiovascular, n (%)	34 (19)	19 (22)	15 (16)	0.278
Steroids, n (%)	5 (3)	3 (4)	2 (2)	0.670
Antiplatelet, n (%)	13 (7)	6 (7)	7 (7)	0.919
Analgesics, n (%)	25 (14)	20 (23)	5 (5)	<0.001
Statins, n (%)	43 (24)	30 (35)	13 (14)	0.001
PPI, n (%)	11 (6)	8 (9)	3 (3)	0.120
Supplement (Calcium/Multivitamin)	17 (9)	16 (19)	1 (1)	<0.001
<b>Number of medications, median (IQR)</b>	<b>5 (4-8)</b>	<b>7 (5-10)</b>	<b>4 (3-7)</b>	<b>&lt;0.001</b>
<b>HIV characteristics</b>				
Time since HIV diagnosis (yr.), median (Range)	8 (4-16)	10 (4-16)	7 (4-16)	0.001
HCV/HBV coinfection, n (%)	34 (19)	18 (21)	16 (17)	0.482
LTBI coinfection, n (%)	21 (12)	9 (11)	12 (13)	0.649
CD4+ count (cells/mm <sup>3</sup> ), n (%)				0.551
<500	80 (44)	40 (47)	40 (42)	
>500	101 (56)	46 (54)	55 (58)	
Viral suppression <50 copies/ml, n (%)	109 (60)	54 (63)	55 (58)	0.502
Number ART, median (Range)	3 (3-6)	3 (3-6)	3 (3-4)	<0.001
<b>Antiretroviral drug class</b>				
NRTIs, n (%)	175 (97)	81 (94)	94 (99)	0.074
INSTIs, n (%)	111 (61)	49 (57)	62 (65)	0.253
NNRTIs, n (%)	51 (28)	21 (24)	30 (32)	0.285
PI, n (%)	47 (26)	42 (49)	5 (5)	<0.001

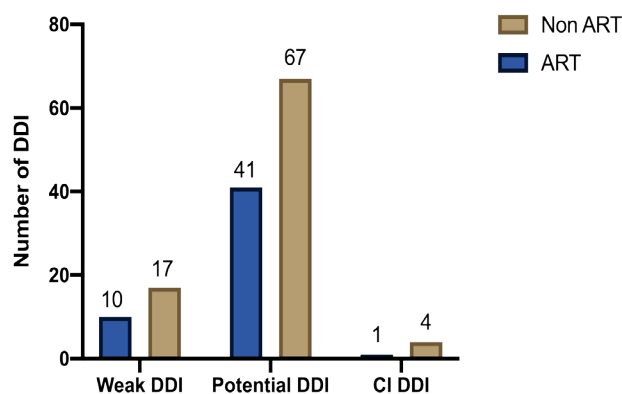
**Abbreviation.** CSDIs, Clinically significant drug interactions; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; INSTIs, Integrase strand transfer inhibitors; LTBI, Latent tuberculosis infection; NNRTIs, Non-nucleoside reverse transcriptase inhibitors; NRTIs, Nucleoside reverse transcriptase inhibitors; PIs, Protease inhibitors; PPIs, Proton pump inhibitors.

Patients were aged between 18-73 years. The median age (SD) was 41±12 years, with the majority being male 132 (73%). Patients with DDIs were older compared to patients with no DDIs (mean ±SD, 43±12 vs 39±11). All patients were receiving a regimen that included at least three ARTs. 175 (97%) of patients were prescribed NRTIs followed by 111 (61%) INSTIs, 51 (28%) NNRTIs, and 47 (26%) PIs.

### Prevalence of Drug interaction

Of 181 patients, 86 (47.5%) patients were identified with antiretroviral agent related drug interactions according to the Liverpool software. A total of 140 potential CSDIs were found in 86 of the 181 study patients. Overall, 27 (19%) interactions were weak, 108 (77%) were potential, and only 5 (4%) were contraindicated interactions with high risk of clinical adverse effects (Figure 1).

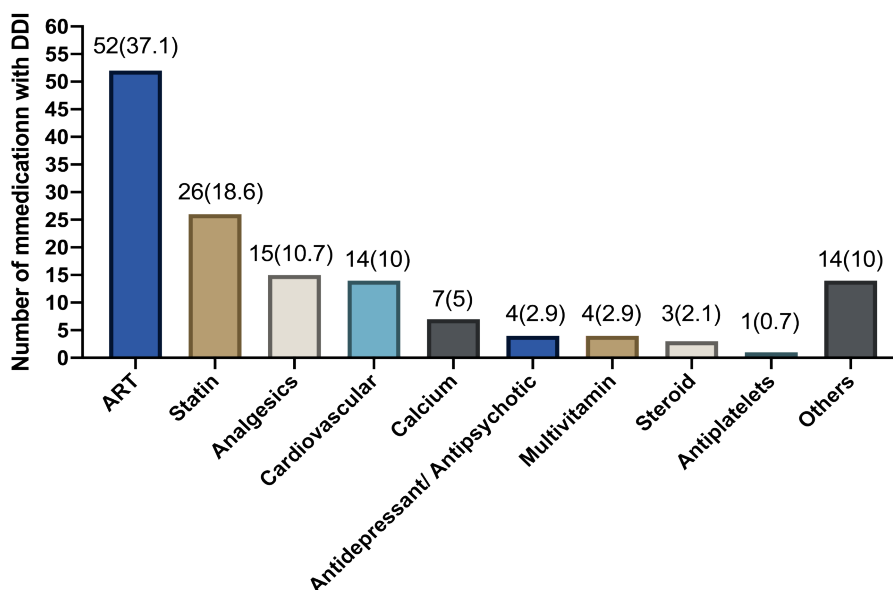
Of the total CSDIs, 52 (37.14%) were between two ARVs, which involved 10 (19%) weak, 41 (79%) potential, and 1 (2%) contraindicated interaction. 88 (62.85%) potential CSDIs were identified between ARV and non-ARV drugs including 17 (19%) weak, 67 (76%) potential, and 4 (5%) contraindicated interactions. The drug interactions found in the 181 HIV patients are presented in figure 1. The most frequent drugs involved potential CSDIs were ARVs (n=52, 37%), followed by statins (n= 26, 19%), analgesics (n=15, 11%), cardiovascular medications (n=14, 10%), calcium supplements (n=7, 5%), and antidepressants/antipsychotics (n=4, 3%). Figure 2 shows the frequency and percentage of CSDIs by drug class in HIV patients.



**Figure 1.** Clinically significant drug interactions between antiretroviral and co-prescribed drugs among HIV infected patients. **Abbreviation.** ART, anti-retroviral therapy; CI, Contraindicated; DDI, Drug-drug interaction. The values are given as the count of DDI.

### Risk factor analysis

In the univariate analysis, patient's age, dyslipidemia, total number of medications, analgesics use, statin use, supplement (multivitamins and calcium) intake, time since diagnosis of HIV, number of ART received, and use of PIs were significant (Table I). However, factors independently associated with CSDIs in the logistic regression model were number of medications (odds ratio [OR] 1.165, 95% CI 1.021-1.329,  $P = 0.023$ ) and the time since diagnosis of HIV (OR 1.156, 95% CI 1.008-1.327,  $P = 0.038$ ) as presented in table II.



**Figure 2.** Percentage of clinically significant drug interactions (CSDIs) by medication among HIV patients

**Abbreviation.** ART, anti-retroviral therapy; DDI, Drug-drug interaction. The values are given as the number of medications with DDI, with the percentage in parentheses.

**Table II.** Independent risk factors of clinically significant drug interactions (CSDIs)>

Characteristics	Adjusted OR (95% CI)	P-value
Age	1.00 (0.95-1.06)	0.881
Male	0.313 (0.098-1.003)	0.051
Number of medications	1.165 (1.021-1.329)	<b>0.023</b>
Time since HIV diagnosis (yr.)	1.156 (1.008-1.327)	<b>0.038</b>

**Abbreviation.** CI, confidence interval; HIV, Human Immunodeficiency Virus; OR, odds ratio.

## Discussion

HIV remains a major global public health issue. It has a low prevalence in the UAE and is estimated to be less than 0.2% among the adult population [14]. The MENA region has a lower prevalence compared to sub-Saharan Africa which has the highest HIV prevalence of all regions. The prevalence of HIV globally is estimated to be 0.8% among adults [15].

There are scarce data on the frequency of CSDIs among HIV patients in the UAE and the Gulf region. ARV therapy increases the risk of drug interactions and, hence, recognition of ARV associated CSDIs is essential for safe and effective prescribing. Our frequency of potential CSDIs (47.5%) was comparable with previous studies from the Netherlands, United States, and Kenya with CSDI reports of 14%–41% HIV patients [6,13,16]. The type of medications most frequently associated with CSDIs varied in different regions. Cardiovascular and CNS medications were mostly associated with CSDIs in the UK, while anti-infective drugs in Kenya and Uganda were more common [9,11,16,17]. In our cohort, potential CSDIs were commonly linked to statins, analgesics, and cardiovascular drugs.

Protease inhibitors and non-nucleoside reverse-transcriptase inhibitors inhibit and induce several important cytochrome P450 isoenzymes that often interfere with the absorption and metabolism of many medications including statins [18,19], cardiovascular medications [20], and psychotropic drugs [21]. Simvastatin and lovastatin are contraindicated with PIs, while pitavastatin and fluvastatin are the safest selection with PIs [18]. For non-nucleoside reverse-transcriptase inhibitors close monitoring is recommended when co-prescribed with high dose of statins [18].

Metabolic syndrome is an adverse effect of both ARVs and antipsychotic medication, therefore patients receiving combination of antipsychotics and PI-based regimen have the greatest risk of development of this side effect [21]. These reactions could be minimized by proper selection and limiting the maximum dose given. Antipsychotics such as olanzapine, risperidone, and quetiapine have strong metabolic adverse effect and can be avoided in those receiving ARV medication [21,22].

Number of medications, which reflect the number of

comorbidities, has been the key determining factor for the incidence of adverse drug reactions and drug interactions [23]. Using logistic regression, the number of medications and time since HIV diagnosis were identified as independent risk factors associated with CSDIs. Some of these factors were related to more complex cases, advanced stages of HIV, and the presence of opportunistic infections.

Results from previous studies have proven that HIV infected populations have a higher prevalence and earlier age of onset for lots of non-communicable diseases (NCDs), such as diabetes mellitus, than age-matched uninfected populations [24]. Treatment for NCDs can cause issues related to polypharmacy, potential DDIs, adverse drug events, loss of treatment efficacy and increase in viral loads of HIV patients [8].

In agreement with previous investigations, the higher number of co-prescribed drugs and PI-containing regimens were associated with significant risk for CSDIs in this study. Our study identified a lower number of comorbidities. This could be attributed to the younger age of this cohort compared to others. Overall, the main HIV comorbidities in the developing regions were infectious disease [25], while cohorts from more developed regions reported metabolic and cardiovascular disorders [26]. In our study, dyslipidemia and statin use was the most common risk factor for occurrence of CSDIs. Lipid disorders are an important health problem in HIV infected patients because HIV and ART provoke metabolic disturbances, increasing insulin resistance levels and significant drug interactions have been reported between ARVs and statin lipid-lowering agents [27]. For example, simvastatin and lovastatin should be avoided in PI-based regimens and safer alternatives must be prescribed [27].

Drug interaction contributes significantly in adverse drug events like drug toxicity and ineffective therapy resulting in increased hospital admissions [28], and healthcare costs as shown in a study among elderly HIV patients in France [29]. Pharmacists play a vital role in HIV patient care: optimizing drug regimens, screening for drug interactions, medication reconciliation, dosage adjustment, reduction in pill burden, recommending alternative therapy, and adherence counseling, which will cause a reduction in hospitalization, cost, morbidity, and mortality [6,30].

The main limitations of this study are: single



centered and retrospective character. In conclusion, our retrospective study shows that the incidence of potential CSDIs is high in HIV-infected people on ART. Awareness of the most common potential CSDIs and risk factors could guide clinicians in identifying patients at high risk of drug interactions. Appropriate management of CSDIs is essential to maximize clinical benefit and minimize potential toxicity. It is important to provide training for all health care workers involved in the medication management of HIV patients including clinicians, nurses, and pharmacists. The electronic alert system has been introduced to facilitate detection of potential drug-drug interaction; however it needs to be further optimized to enhance detection of serious interaction and remove the unspecific false warnings that could cause alert fatigue [31,32].

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