

Original Research Article

Concurrent use of drugs and potential drug interactions in HIV-infected patients in a tertiary healthcare facility in Turkey

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Abstract

Purpose: To investigate the frequency of concurrent drug use and drug interactions in patients with human immunodeficiency virus (HIV) infection.

Methods: The medical records of HIV-infected patients followed up at Ondokuz Mayıs University Hospital in the last six months were retrospectively reviewed to assess the antiretroviral therapy (ART) regimens used, the prescribed concurrent drugs, and their interactions

Results: The records of 268 patients were evaluated; of these, 43 (16 %) were women, and 225 (84 %) were men. The mean age of the patients was 43.8 ± 12.1 years. Concurrent drugs were prescribed to 210 (78.3 %) patients. Drug interactions were detected in 115 (42.9 %) patients. Of the 210 drug interactions detected, 168 (80 %) were potential interactions, 39 (18.6 %) were weak interactions, and 3 (1.4 %) were contraindicated. A statistically significant relationship was not observed in gender, age, and rate of concurrent drug prescription. Increased nephrotoxicity was the most common potential drug interaction. Non-steroidal anti-inflammatory drugs were the most commonly prescribed class of drugs along with ART.

Conclusion: Physicians treating HIV-infected patients should be conscious of, and careful about the concurrent use of drugs and their potential drug interactions.

Keywords: AIDS, HIV, ART (Antiretroviral therapy), Drug-drug interactions, Polypharmacy

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INTRODUCTION

Since its emergence, human immunodeficiency virus (HIV) infection has accounted for the death of approximately 33 million people and continues to be a significant global public health problem. Because of the efforts of the society and initiatives taken by the government to prevent new HIV infections and increased access to

diagnosis, treatment, and health care services, HIV infection has become a manageable chronic health condition, allowing patients with HIV infection to live long and healthy lives. At the end of 2019, approximately 38.0 million people had an active HIV infection, and approximately 68% of adults and 53% of children were on antiretroviral therapy (ART) [1]. ART significantly increased the survival in HIV-infected patients and brought life expectancy rates closer to those

of the average population. ART consists of a combination of drugs from different drug classes, and HIV-infected patients often use additional drugs for acquired immunodeficiency syndrome (AIDS)-related infections and other chronic diseases related to ageing, resulting in the consumption of multiple drugs [2,3]. One of the biggest challenges of multi-drug regimens is their interactions, which are classified as pharmacokinetic and pharmacodynamic interactions. Although some of the interactions are weak, some are potentially significant, leading to severe toxicity and treatment failure [4]. In addition, because of the increasing age of the HIV-infected patients, the increasing burden of traditional chronic diseases such as diabetes and hypertension, these patients are at significant risk of drug-related adverse events [5].

In countries where ART is accessible to people living with HIV and where there are healthcare facilities that allow regular follow-up of treatment, managing the use of drugs administered concurrently with ART has become an independent issue for both physicians and patients. This study examined the frequency of concurrent drug use and drug interactions in HIV-infected patients on different ART regimens.

METHODS

The medical records of patients of Ondokuz Mayıs University Hospital aged 18 years and older and were diagnosed with HIV infection between January 2005 and October 2019 were retrospectively reviewed. The social security prescription database was used to identify the concurrent drugs prescribed in the last six months. The study did not include children under the age of 18 years, patients who were not on ART, and patients whose data on concurrent drug use were not available.

An automated electrochemiluminescent immune-assay method (Cobas e411, Roche Diagnostics) was used to determine serological markers of HIV infection in all patients included in the study. The definitive diagnosis of HIV infection was accepted as the presence of reactive HIV 1/2 antigen/antibodies confirmed by a verification method in a central public health laboratory authorized by the Ministry of Health.

The latest version of the Liverpool University HIV drug interaction database was used to query for drug interactions [6]. Only drug interactions between the ART and concurrent drugs were evaluated. The results of interactions were classified into four different categories: If the

interaction between the drug pairs led to serious side effects or a lack of therapeutic effect, they were classified as 'contraindicated', if they could be managed by changing the dosage or close monitoring, they were classified as 'potential interactions', if they did not require further management, they were classified as 'weak interactions' and as no interaction detected.

Ethical approval for the study was obtained from the Ondokuz Mayıs University Clinical Research Ethics Committee (approval no. July 2020/410-477). This study was conducted according to the ethical standards of the 1975 Helsinki Declaration, which was revised in 2008 [7].

Statistical analysis

Statistical analysis was performed using SPSS 20.0 software for Windows (SPSS, Chicago, IL). Data were presented as mean \pm standard deviation (SD) or N (percentage). The Chi-square test was used for determining the relationships between categorical variables. Mann Whitney U test was used to compare nonparametric test outcomes between two independent groups. Statistical significance was accepted with a P-value < 0.05 .

RESULTS

A total of 268 patients, including 43 (16 %) women and 225 (84 %) men, were followed up in the last six months at the Ondokuz Mayıs University Hospital. The mean age of the patients was 43.8 ± 12.1 years. The initial mean CD4 T lymphocyte count was $363.7 \pm 244.4/\text{mm}^3$. The plasma HIV-1 ribonucleic acid (RNA) load at the time of diagnosis was 143,719 (28–330,000,000) copies/mL. A possible route of transmission was determined to be heterosexual intercourse in 178 (64.1 %) patients and homosexual/bisexual intercourse in 64 (23.8 %) patients. Of the 268 patients, 256 (95.5 %) were on the triple-drug ART, the backbone of which consists of two nucleoside reverse transcriptase inhibitors (NRTIs) and a third agent belonging to other drug classes, 11 (4.1 %) was on the dual-drug ART, and 1 (0.4 %) was on the quadruple-drug ART.

The prescription query database showed that 210 (78.3 %) patients had been prescribed one or more concurrent drugs in the last six months. Of the 210 patients who had been prescribed concurrent drugs, 37 (17.6 %) were women, 173 (82.4 %) were men, and their mean age was 44.4 ± 11.1 years. No statistically significant relationship was observed between gender, age, and concurrent drug prescription rates ($p = 0.1$ and $p = 0.182$). No drug interactions were

observed in 95 patients, whereas a total of 210 drug interactions were detected in 115 (42.9 %) patients. Of these 210 interactions, 168 (80 %) were potential interactions, 39 (18.6 %) were weak interactions, and 3 (1.4 %) were contraindicated.

Table 1: Antiretroviral regimens

Antiretroviral regimen	n (%)
1- Triple therapy	256 (95.5%)
1.1 Backbone therapy (Dual NRTI)	
TDF/FTC	148
ABC/3TC	82
TAF/FTC	24
ZDV/3TC	2
1.2 Third Agents	256 (95.5%)
Integrase strand transfer inhibitors	
DTG	170
EVG/COBI	40
RAL	3
Protease inhibitors	
LPV/RTV	9
DRV/RTV	6
Non-NRTISs	
EFV	28
2- Dual therapy	11 (4.1%)
DTG/3TC	6
DTG+DRV/RTV	3
DTG+LPV/RTV	1
RAL+ DRV/RTV	1
3- Quadruple therapy	1 (0.4%)
ZDV/3TC +RTV+DTG	1

NRTI, nucleoside reverse transcriptase inhibitors; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; ABC, abacavir; 3TC, lamivudine; TAF, tenofovir alafenamide; ZDV, zidovudine; DTG, dolutegravir; EVG, elvitegravir; COBI, cobicistat; RAL, raltegravir; LPV, lopinavir; RTV, ritonavir; EFV, efavirenz

Increased nephrotoxicity due to the concurrent use of Tenofovir disoproxil fumarate (TDF) and non-steroidal anti-inflammatory drugs (NSAIDs) accounted for 60.1 % of the potential interactions while increased metformin level in the blood due to the concurrent use of dolutegravir with metformin accounted for 7.7 % and the second most common of the potential interactions.

Increased lamivudine (3TC) blood levels due to the concurrent use of trimethoprim/sulfamethoxazole (TMP/SMX) and 3TC accounted for 25.6 % and were the most common of weak interactions.

Contraindications were reported for three (1.1 %) patients who were on cobicistat containing ART regimens. Of these three patients, two patients

have been prescribed quetiapine and one has been prescribed clopidogrel.

NSAIDs, prescribed to 53.8% of the patients, were the most frequently prescribed concurrent drugs. The next most commonly prescribed drugs were systemic anti-infectives (16.1 %) and oral antidiabetics (6.6 %), cardiovascular system drugs (5.8 %), nervous system drugs (5.8 %), and other drugs belonging to different classes (11 %).

DISCUSSION

ART has significantly increased the life expectancy of HIV-infected patients. However, the presence of comorbid diseases, opportunistic infections, and non-AIDS-related malignancies in this patient group has increased. The number of drugs used concurrently with ART for these comorbid conditions increases the risk of potential drug interactions [8].

A total of 26,164 HIV-infected patients were identified in Turkey between 1985 and 2019. These patients were mostly in the 30 – 39 years age group, 80.72 % of the patients were men, and 19.28% were women [9]. In our study, the gender distribution was similar to the national data. Since our study was based on the age of the patients at the time of the study conducted, the mean age was found to be higher than the national data.

All the patients were on ART regimens recommended by national and by international guidelines, mostly in which two agents from the NRTIs and one agent from the Integrase strand transfer inhibitors (INSTIs), Protease inhibitors (PIs) or Non-nucleoside reverse transcriptase inhibitors (NNRTIs) group were combined [10-12].

In a prospective study conducted in Switzerland with 1497 HIV-infected patients aged 16 years and older, 68 % of the patients used concurrent drugs in addition to ART within six months of being enrolled in the study. The results of this study showed that potential drug interactions in 40 % of the patients, 59 % of these interactions required potential dose adjustment and/or close monitoring, and 2 % were contraindicated. Further, female gender and advanced age were risk factors for multiple concurrent drug use in this study [13].

In a study conducted in Belgium with 145 patients who started ART in a single HIV clinic from January 2009 to April 2016, 78 % of the patients used concurrent drugs during the follow-up period, of these concurrent drugs, 63 % had

potential interactions, and 1 % of these interactions have been reported to be as contraindications. Further, 26 % of the patients concurrently used five or more drugs, and concurrent drug usage was correlated with increased age. No difference was observed in the frequency of drug interactions in terms of age and gender [14].

In an observational study conducted between March 2015 and March 2016 in Barcelona, Spain, that included all HIV-infected patients aged 18 years and over, 70 % of patients had concurrent drug use, and potential drug interactions were detected in 44.7 % of patients. The potential interactions were classified as moderate and severe in 59.2% and 4.3% of the patients, respectively. The mean age of patients with drug interactions was higher than those without interactions, but no difference was observed in drug interactions in terms of gender [15].

HIV-infected patients, who constitute the patient population of the studies across countries, have different age, gender and risk factors that may affect the number of concurrent drugs and the frequency of interactions. Although varying results were reported in the studies conducted thus far, the frequency of concomitant drug use and drug interaction was considerably high in all studies.

TDF-emtricitabine (TDF/FTC) was the most frequently preferred combination in the backbone treatment, and TDF alone accounted for more than half of the drug interactions. TDF/FTC is a prodrug that metabolizes to tenofovir (TFV) in plasma. TFV is primarily eliminated via the kidney by glomerular filtration and active tubular secretion. TFV is taken up to the proximal-tubule cells by human organic anion transporter 1 (hOAT1) and then actively secreted into the tubular lumen by multidrug-resistance protein-4 (MRP-4) [16]. NSAIDs (e.g., ibuprofen, indomethacin, and probenecid) which increase the toxicity risk of TFV by inhibiting the drug transport function of MRP4, were the most frequently prescribed concomitant drugs in our patient group. Further, NSAIDs may potentially contribute to the development of further kidney damage by reducing glomerular filtration [16,17]. Since a majority of drugs in the ART regimens were eliminated via renal excretion and NSAIDs were the most commonly prescribed concomitant drugs, nephrotoxicity, the most frequently reported potential drug interaction, was an expected outcome. FTC in the TDF/FTC combination is generally well tolerated with the

NSAIDs, and no interaction between the NSAIDs was reported.

DTG, which prevents the viral genome from entering the host DNA by blocking the activity of the HIV viral integrase enzyme, was the most frequently used drug combined with the backbone of ART in our study. DTG inhibits the organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE 1) pathways, which are known to play a role in metformin excretion, and may increase the plasma concentration of metformin [18]. An increase in the blood level of metformin with concurrent use of DTG was the second most common potential drug interaction detected in this study. The risk of diabetes mellitus is twofold greater in patients with HIV than in the general population [19]. Thus, because of the higher prevalence of diabetes in HIV-infected patients, the interaction of DTG and metformin may be frequently expected. Thus, caution should be exercised regarding serious clinical consequences.

The most commonly detected weak interaction, an increase in 3TC blood levels, was reported in ten patients who were on 3TC containing ART regimen, concurrently prescribed for TMP-SMX. TMP-SMX reduces HIV-related mortality in adults and children when used as a prophylactic against opportunistic infections due to HIV infections [20]. Besides, TMP-SMX is a drug indicated for the treatment of common infections such as acute infective exacerbation of chronic bronchitis and urinary tract infections. [21]. Co-administration of TMP-SMX and 3TC has been shown to increase the plasma concentrations of 3TC. Although this interaction is not reported to cause a significant increase in concentration-related toxicity at the doses studied, awareness of these commonly used drug groups is important.

In our study, three patients had contraindications between ART regimens and concurrent drugs. Two of the patients were prescribed quetiapine, an antipsychotic drug, and the other, clopidogrel, an antiplatelet drug used to reduce the risk of heart disease and stroke. Concomitant use of quetiapine is contraindicated due to the potential increase in exposure to quetiapine with ART regimens containing cobicistat, as CYP3A4 metabolism is inhibited by cobicistat [6]. An ART consisting of cobicistat in HIV-infected patients showed a 69 % reduction in the level of active metabolites of clopidogrel compared to that in healthy volunteers [22]. Epidemiological studies have shown that rates of psychiatric disorders such as substance abuse, depression, post-

traumatic stress disorder, and psychosis in the HIV-infected population are 1.5 to 8 times higher than in the general or the non-HIV infected population [23]. HIV infection is considered a prothrombotic condition, and it has been shown those thrombotic events maybe ten times more common in this group than in the general population [24]. These results have shown that HIV-infected patients with psychiatric comorbidity or thrombotic disorders, especially those who are on boosted antiretroviral therapy, may be at serious risk of potential drug-drug interactions.

Limitations of the study

The number and types of drug groups used according to the age and gender of the patients were not defined separately, and the use of over-the-counter drugs was not assessed in this study. Comprehensive studies should be performed to obtain more information about the clinical and laboratory findings of drug interactions after the use of concurrent drugs. These are considered limitations of the present study.

CONCLUSION

The findings of this study show that a significant number of patients have been prescribed concurrent drugs in the six months of the study, and almost half of the patients are at potential risk of drug interactions. Physicians treating HIV-infected patients should be cautious about the use of drugs concurrently with ART and their potential drug interactions.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this study.

Contribution of authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Bilek and Deveci designed the study. Bilek and Şensoy performed practical work. Bilek, Deveci and Tanyel analyzed the data. Bilek wrote the

manuscript, which was also reviewed by Deveci and Tanyel.

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