LETTER TO THE EDITOR / EDİTÖRE MEKTUP

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HIV/AIDS Treatment is Easier But Drug-Drug Interactions?

HIV/AIDS Tedavisi Kolaylaştı, Peki İlaç-İlaç Etkileşimi?

Hüsnü PULLUKÇU, Gülşen MERMUT, Tansu YAMAZHAN, Deniz AKYOL, Meltem IŞIKGÖZ TAŞBAKAN

Ege University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, İzmir, Turkey

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Anahtar Kelimeler: Salmoterol, HIV, AIDS, flutikazon, darunavir kobisistat

Dear Editor,

With recent advances, HIV infection has become a treatable chronic disease. Current antiretroviral (ARV) therapy (ART) provides more rapid viral suppression with less side effects. Since currently therapy is initiated early, individual treatment plans are made in consideration of long-term side effects such as bone toxicity, renal toxicity, dyslipidemia, insulin resistance, and cardiovascular disease. Interactions between drugs used by patients to treat comorbid diseases and their current ART regimen are also important. Monitoring for these problems and for drug-drug interactions are primary concerns in patient follow-up[1,2].

Interaction between ARVs and concomitant medications has been reported at rates of 14-41%[3]. Drug-drug interaction is common in HIV-infected patients because these drugs act as drug metabolism enzyme inducers or inhibitors. Drug-drug interactions in patients receiving ART may lead to toxicity, drug resistance, and changes in the therapeutic level of the drug. Therefore, it is important to consider potential interactions to ensure effective viral suppression and minimal toxicity. It was reported that 70% of the 1.259 HIV-infected patients in Spain (from March 2015 to September 2016) used co-medications, and drug-drug interactions occured in 44.7%[3]. In this paper, we present the development of an unexpected drug-drug interaction in a patient starting ART and how it was managed.

A 22-year-old female patient who was infected with HIV through unprotected sexual intercourse presented to our clinic for follow-up. She had no history of cigarette, alcohol, or drug use. Physical examination and routine laboratory tests revealed no pathological findings. Treatment was initiated with elvitegravir + cobicistat + tenofovir + emtricitabine (EVG/c/TDF/FTC). At start of treatment, viral load was 12,767 copies/ml, CD4 lymphocyte count was 280/mm^3, and no resistance to ARV was detected. The patient presented with complaints of facial swelling and abnormal hair growth on the forehead, back of the neck, and back In the 3rd month of treatment. Laboratory test results showed ACTH: 637 pg/ml (normal: <46) and cortisol: <0.4 µg/dl (normal: 5-25). Oral hydrocortisone 50 mg/day was started for suspected partial adrenal insufficiency. When questioned about the use of other medications, the patient reported using an inhaled preparation containing 50 µg of salmeterol and 250 µg of fluticasone propionate for asthma, which she had not previously mentioned. Suspecting a possible drug-drug interaction, the website https://www.hiv-druginteractions.

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Address for Correspondence/Yazışma Adresi: Deniz Akyol MD,
Ege University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, İzmir, Turkey
E-mail: denizakyol416@gmail.com **ORCID:** orcid.org/0000-0002-1644-6248

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org was searched. It was learned that coadministration of fluticasone propionate with the patient's current ART might reduce serum cortisol concentrations and that increased salmeterol concentrations might cause cardiovascular side effects (prolonged QT, sinus tachycardia, palpitations). Although the patient was responding well to ART, with no detectable viral load and CD4 lymphocyte count of 459/mm^3 after 3 months of treatment, her regimen was changed to abacavir + lamivudin + dolutegravir. Hydrocortisone therapy was tapered and discontinued over 3 months. The patient showed improvement in clinical and laboratory findings, with no detectable viral load and CD4 lymphocyte count of 629/mm^3 after 1 year of ART, and she is still continuing treatment with the same regimen.

ART is a complex form of treatment that HIV-infected patients must use for life. Until recently, guidelines have presented different recommendations regarding the timing of ART initiation depending on factors such as disease stage, CD4 lymphocyte count, and viral load[4,5]. However, the recommendations changed in accordance with the results of the START and TEMPRANO studies published in 2015, and it is now recommended to initiate ART as soon as possible after the infection is detected, regardless of CD4 lymphocyte count[1,2,6,7]. However, it is very important to take a detailed history before starting this therapy because treatment adherence, drug interactions, and access to healthcare facilities will influence a patient's treatment. It is the primary duty of clinicians to best know and interpret the pharmacokinetic and pharmacodynamic activities of the drugs used. As seen in our case, however, drugs used via non-oral routes (inhalation, intranasal, topical, etc.) may not be mentioned because the patient does not attach importance to them.

In a study evaluating drug interactions in HIV patients, 268 patients on ART were followed for 5 months, during which 292 possible drug-drug interactions were detected. Of these, 34.9% (102 patients) were classified as serious clinical drug interactions. Drug-drug interactions with ART were documented in 54 of the 102 patients. The drugs most commonly involved in interactions were protease inhibitors (PI), benzodiazepines, non-steroidal anti-inflammatory drugs, steroids, antithrombotics, and proton pump inhibitors (PPI)[8]. The study showed that using more than 5 drugs and using PI were independent risk factors.

Studies have shown that adverse event management would be more successful in terms of detecting drug-drug interactions, arranging the content of prescriptions, and ensuring patient safety if HIV-infected patients' ART and co-medications were registered and evaluated by a team of physicians and clinical pharmacologists experienced with HIV[3].

Similar to our case, Wassner et al.[9] reported the development of secondary iatrogenic adrenal insufficiency following intralaminar epidural spinal injection of triamcinolone acetonide due to persistent back pain despite the use of painkillers in a HIV-infected patient using EVG/c/TDF/FTC.

Drug interactions should be considered when ART is initiated or changed. Interactions of drugs included in the ART regimen as well as co-medications should be evaluated, and if a drug that causes interaction is prescribed, the physician should closely monitor for both efficacy and concentration-related toxicities. Drug interactions may necessitate drug changes even if treatment is successful[1]. As in our case, drug interaction led to a change in ART despite effective viral suppression.

Drug interactions can be categorized as those that alter the absorption, the hepatic metabolism, and the pharmacokinetics of a drug. Drug absorption is primarily affected by PPI, H_2 receptor antagonists, and antacids. Hepatic metabolism is affected through the cytochrome P450 enzyme system and the uridine diphosphate-glucuronosyltransferase 1A1 enzyme systems, which are responsible for the metabolism of many drugs[1]. Some medicines may be involved in different reactions. In the present case, we believe that the inhaled fluticasone used for asthma interacted with EVG/c/TDF/FTC, which contains the potent CYP3A inhibitor cobicistat, to reduce serum cortisone levels and this might have resulted in adrenal insufficiency. The fact that all the medications our patient was using for asthma prior to ART initiation were not learnt and the resulting failure to monitor blood cortisol levels were shortcomings in the management of this case.

In conclusion, patients with HIV infection require not only evaluation of short-term virologic and immunologic improvement with their existing ART, but must also be closely monitored for comorbidities, drug interactions, and side effects. Topical and inhaled preparations in particular are often not reported by patients. Considering that these therapies may also cause drug-drug interactions, patients should be questioned in detail about the medications they use.

Ethics

Informed Consent: A consent form is not needed for this submission.

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Authorship Contributions

Concept: H.P., M.I.T., T.Y., Design: M.I.T., H.P., G.M., Data Collection or Processing: M.I.T., G.M., Analysis or Interpretation: H.P., T.Y., M.I.T., Literature Search: G.M., M.I.T., Writing: G.M., M.I.T., D.A.

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