Effect of drug interactions involving antiretroviral drugs on viral load in HIV population

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ABSTRACT

Background Most studies focus on potential drug interactions, without considering the effect of these on the response to antiretroviral (ARV) therapy. We assess the effect of potential drug–drug interactions (pDDIs) that could have lowered the ARV concentration (pDDI-lowerARV) on HIV viral load.

Methods Retrospective observational cohort study was conducted on all HIV-infected outpatients attending the Pharmacy Service of a regional reference hospital in Murcia (south-eastern Spain). The complete treatment was subsequently screened for pDDIs using the database 'InteraccionesHIV.com'. The study focused on interactions involving at least one ARV drug and, especially, any pDDI-lowerARV.

Results Two hundred and twenty-nine patients were included in the study. A total of 168 pDDIs were identified, of which 62 (36.9%) had the potential to lower ARV concentrations. In 77% of cases, the drug involved in the reduction of plasma concentrations was a protease inhibitor (PI), and in the rest of the drug interactions the ARV drug affected was a non-nucleoside reverse-transcriptase inhibitor. Baseline viral suppression was noted in 57.1% of patients with pDDI-lowerARV compared with 61.5% of patients without pDDI-lowerARV ($p=0.605$), and in 85.7% versus 79.7%, respectively, after a 24-week follow-up period ($p=0.516$).

Conclusions This study shows that prevalence of pDDI-lowerARV was high; however, no association was found between the presence of these interactions and virological failure. These results confirm the need for further studies to understand the consequences of interactions in real-life clinical practice, since most pharmacokinetic studies tend to evaluate the ability of interaction between two drugs under controlled conditions.

BACKGROUND

Drug–drug interactions are one of the most common drug-related problems, frequently leading to the occurrence of undesirable side effects and/or compromising the effectiveness of treatment.^{1–3} Clinically significant drug interactions involving antiretroviral (ARV) agents have been reported in 20%–40% of HIV-positive patients.^{2–4} However, most studies^{2–6} focus on potential drug–drug interactions (pDDI), without considering the effect of these on the response to ARV therapy (ART). In this study, our goals were to determine the prevalence of pDDIs that could have lowered the ARV concentration (pDDI-lowerARV) and to assess the effect of these interactions on the HIV viral load.

METHODS

Retrospective observational cohort study was conducted on all HIV-infected outpatients attending the Pharmacy Service of a regional reference hospital in Murcia (south-eastern Spain), which provides medical care to 196 000 subjects.

Eligibility criteria included HIV-positive patients aged 18 years or older and had at least one active prescription for an ARV drug at the time of data collection (May–September 2013). We included ARV treatment-naïve and ARV treatment-experienced patients. Every patient was followed up for 24 weeks after starting combination ART. Patients were excluded if they were enrolled in a clinical trial or if there was no information relating to the concomitant treatment or laboratory parameters (including CD4 cell counts and viral loads).

Patient data (gender and age), laboratory values and information about an ARV drug's resistance profile were abstracted from medical records. Information on ARV drug therapies being received was obtained by reviewing the medical prescription and computer consultation using the application Agora Plus to ascertain the treatment prescribed in primary care. The researchers reviewed any concomitant treatment being received before beginning combination ART.

For combination drug products, each individual active ingredient was counted as a separate drug. Ritonavir was not counted as a separate drug. The adherence to ARV treatment through dispensing records was calculated as number of medications dispensed/number of medications prescribed, multiplied by 100, during the follow-up period. Patients were considered adherent if ART adherence through dispensing records was >90%.

The complete treatment was subsequently screened for pDDIs using the database 'InteraccionesHIV.com', which was developed by the Agustí Pi i Sunyer Medical Research Institute in collaboration with several scientific societies.⁷ In this database, pDDIs are classified according to their severity. These explain the mechanism of each drug interaction and, in certain cases, can provide the recommended course of action to manage the interaction. The study focused on interactions involving at least one ARV drug and, especially, any pDDI-lowerARV.

Our primary clinical outcome was viral suppression at 24 weeks of follow-up period. Viral suppression was defined as an HIV viral load <50 copies/mL, and this was recorded at start of combination ART (baseline) and after a follow-up period of 24 weeks. We consider virological failure

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when virological suppression is not achieved after the follow-up period.

A descriptive analysis was established for the above mentioned variables, expressing the quantitative data in terms of mean and SDs, and qualitative data in terms of frequency and percentages. Quantitative variables were compared using Student's *t* test or non-parametric Mann–Whitney *U* test, as appropriate, verified by Kolmogorov–Smirnov test. Differences in qualitative variables were assessed by Fisher's exact test. All procedures were developed using SPSS V.15.0 software.

RESULTS

Of the 298 patient records screened, 229 (76.8%) were included in the analysis, while 54 were excluded because the authors did not have access to the laboratory parameters (including CD4 cell counts and viral loads) and/or the concomitant treatment, while another 15 were excluded because they were taking part in a clinical trial. Patients were aged 21–81 years (median age, 45.6 years): 167 (72.9%) were men and 62 (27.1%) were women (table 1).

A total of 1450 drugs were recorded, of which 47.3% were ARV drugs. Most patients (97.8%) were receiving a combination ART that included at least three active ARV agents. Of the 229 patients, 110 (48.0%) were receiving protease inhibitor (PI)-based regimens, 99 (43.2%) were receiving non-nucleoside reverse-transcriptase inhibitor (NNRTI)-based regimens, 9 (3.9%) were receiving nucleoside reverse transcriptase inhibitor (NRTI)-based regimens and only 8 (3.5%) were receiving a PI plus NNRTI regimen. Finally, two patients were receiving integrase inhibitor-based regimens and one patient was receiving monotherapy with lopinavir/ritonavir.

A total of 168 pDDIs were identified, of which 62 (36.9%) had the potential to lower ARV concentrations. These occurred in 42 patients, indicating that 18.3% of the study population had at least one pDDI-lowerARV. In 77% of cases, the drug involved in the reduction of plasma concentrations was a PI,

and in the rest of the drug interactions the ARV drug affected was an NNRTI.

The most prevalent drug combinations involved in pDDI-lowerARV were atazanavir-tenofovir (14.4%), darunavir-etravirine (6.1%), atazanavir-omeprazole (5.7%), tipranavir-omeprazole (0.4%) and nevirapine-atazanavir (0.4%).

Baseline viral suppression was noted in 57.1% of patients with pDDI-lowerARV compared with 61.5% of patients without pDDI-lowerARV ($p=0.605$), and in 85.7% versus 79.7%, respectively, after a 24-week follow-up period ($p=0.516$). The mean change in viral load was similar in both groups (decrease in viral load, 2.65 $\log_{10}$ copies/mL vs 2.95 $\log_{10}$ copies/mL, respectively; $p=0.659$). In 6/33 cases of interaction between tenofovir and atazanavir, virological suppression was not achieved after 24 weeks of follow-up. Virological suppression was achieved in all other cases of pDDI-lowerARV. The CD4 T-cell count after 24 weeks did not differ between the patients with and without pDDI-lowerARV (580.4 vs 591.8; $p=0.136$). No drug resistance mutations were detected in this group of patients and the adherence to ART was similar in both groups (table 1).

DISCUSSION

This study shows that prevalence of pDDI-lowerARV was high, affecting nearly a quarter of the study population. However, no association was found between the presence of these interactions and virological failure.^{8–9} We also agree with other authors^{2–3–5–8–9} that the PIs are drugs most commonly involved in interactions, atazanavir being the most prevalent in our study.

When the clinical consequences of the interactions were analysed, the results were not as expected according to the available evidence.^{1–10} For example, according to the available evidence, the coadministration of tenofovir and atazanavir should not impair the plasma concentrations of ritonavir-boosted atazanavir; however, in our study, we observed that virological failure occurred in 18.2% (6/33) of cases. Given that no drug resistance

Table 1 Characteristics of HIV-infected patients and outcomes of the effect of drug interactions on viral load

	pDDI-lowerARV (n=42)		NO pDDI-lowerARV (n=187)		p Value
	Mean	(SD)	Mean	(SD)	
Age (years)	46.1	(9.3)	45.5	(9.4)	0.692*
Number of antiretroviral agents	3.0	(0.2)	3	(0.2)	0.997†
Total number of drugs	7.2	(4.4)	6.1	(4.2)	0.057†
Baseline CD4 T-cell count	476.8	(315.4)	541.8	(331.1)	0.136†
Baseline viral load, $\log_{10}$ copies/mL	5.2	(6.1)	4.6	(5.2)	0.697†
Viral load at 24 weeks of follow-up, $\log_{10}$ copies/mL	4.0	(4.8)	4.1	(5.1)	0.502†
Adherence	92.7	(9.8)	91.5	(15.1)	0.962*
	Subjects (n)	(Per cent)	Subjects (n)	(Per cent)	p Value
Male	28	(66.7)	139	(74.3)	0.339‡
Baseline viral load <50 copies/mL	24	(57.1)	115	(61.5)	0.605‡
Antiretroviral drug regimen					
2 NRTI+PI/r	33	(78.6)	73	(39.0)	<0.01‡
2 NRTI+NNRTI	0	(0.0)	97	(51.9)	<0.01‡
3 NRTI	1	(2.4)	6	(3.2)	0.620‡
Virological failure at 24 weeks of follow-up	6	(14.3)	38	(20.3)	0.156‡

*Differences in quantitative variables by Student's *t* test.

†Differences in quantitative variables by Mann–Whitney *U* test.

‡Differences in qualitative variables were assessed by Fisher's exact test.

NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; pDDI-lowerARV, potential drug–drug interactions that could have lowered the antiretroviral concentration; PI, protease inhibitor.

mutations were detected and that adherence to ART was similar in both groups, the virological failure in these patients could be due to the interaction between both the drugs. In addition, most of the currently available drug interaction databases advise against the combination of omeprazole and atazanavir; however, our study shows that the virological suppression was achieved in all patients. These a priori controversial results confirm the need for further studies to understand the consequences of interactions in real-life clinical practice, since most pharmacokinetic studies tend to evaluate the ability of interaction between two drugs under controlled conditions.

There are several limitations to our study. The ARV plasma levels were not available to establish an adequate causal relationship between the concentration and the effect on viral load. It should be noted that the determination of plasma concentrations of ARV is not routinely performed in most Spanish hospitals. Another limitation in our work involves the lack of comparisons made with the findings of other studies because of the variability in the tools available for detecting drug interactions. In our case, we used HIV-specific database, 'InteraccionesHIV.com,' which was developed by the Agustí Pi i Sunyer Medical Research Institute in collaboration with the AIDS Study Group of the Spanish Society of Clinical Microbiology and Infectious Diseases and the Spanish Society of Hospital Pharmacy, among others.⁷

It should be emphasised that this is the first study to examine the clinical consequences of drug interactions in HIV-infected patients since most studies focus exclusively on potential clinically significant drug interactions.^{2–6} The authors consider the findings interesting because the HIV-infected outpatients receiving ARV drugs belonging to the healthcare area in question were included in the study. The fact that the demographic, clinical and therapeutic regimens in the present study are similar to those described by other authors increases the validity of our results.

Since the concomitant use of ARV drugs and wide variety of drugs for comorbidities is increasing, further well-conducted studies are necessary on drug interactions in clinical practice, involving HIV-infected patients to provide definitive answers about the safety and efficacy of these drug combinations.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The study was approved by the local Ethical Research Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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