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Potential interactions in a cohort of elderly HIV-positive patients

Interacciones potenciales en una cohorte de pacientes VIH positivos de edad avanzada

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Abstract

Objective: An increased life expectancy leads to a new model of HIV patient with chronic diseases and occasionally polymedicated. With this study, we intend to understand treatment complexity and to identify any potential interactions between antiretroviral drugs and home medication in our patients, in order to identify and prevent them.

Method: A retrospective, descriptive study carried out in a cohort of > 50-year-old patients on antiretroviral treatment in a tertiary hospital.

Results: We included 242 patients; 148 (61%) of them were receiving some concomitant treatment. We detected 243 potential interactions: 197 considered moderate and 46 severe, in 110 patients.

Of the severe interactions, 35 (76%) were related to boosted protease inhibitors.

The main consequence of these interactions was an increase in the plasma concentrations of the home medication (48%).

Statins (24%) were the group most involved in severe interactions, followed by inhaled corticosteroids (15%).

Conclusions: Practically half of patients were polymedicated, and a high number of potential moderate or severe interactions were observed. The Hospital Pharmacist must play an essential role in their detection, management and early communication.

Resumen

Objetivo: El aumento de la esperanza de vida conduce a un nuevo modelo de paciente VIH positivo, con enfermedades crónicas y, en ocasiones, polimedicado. Pretendemos con este estudio conocer la complejidad de los tratamientos e identificar potenciales interacciones entre antirretrovirales y medicación domiciliaria de nuestros pacientes, con objeto de tenerlas identificadas y poder prevenirlas.

Método: Estudio descriptivo, retrospectivo, en una cohorte de pacientes con tratamiento antirretroviral mayores de 50 años en un hospital de tercer grado.

Resultados: Se incluyeron 242 pacientes, de los que 148 (61%) recibían algún otro tratamiento. Detectamos 243 potenciales interacciones: 197 consideradas moderadas y 46 graves; afectando a 110 pacientes.

De las graves, 35 (76%) se relacionaron con inhibidores de proteasa potenciados. La principal consecuencia fue un aumento de las concentraciones plasmáticas del tratamiento domiciliario (48%). Las estatinas (24%) fueron el grupo especialmente implicado en las interacciones graves, seguidas de los corticoides inhalados (15%).

Conclusiones: Prácticamente la mitad de los pacientes estaban polimedicados, observándose un elevado número de potenciales interacciones moderadas o graves. El farmacéutico de hospital debe jugar un papel crucial en su detección, manejo y comunicación precoz.

KEYWORDS
HIV; Antiretroviral therapy; Aging; Drug interactions.

PALABRAS CLAVE
VIH; Tratamiento antirretroviral; Envejecimiento; Interacciones medicamentosas.

Introduction

The armamentarium available for treating the Human Immunodeficiency Virus (HIV) is increasingly larger and more effective; said population presents overall survival rates very superior to those recorded in previous years[1,2].

This increase in life expectancy entails, logically, an increase in comorbidities: those inherent to age and those that might be associated with the infection[3,4]. Currently, the management of this concomitant medication represents a challenge for clinicians at the time of initiating an antiretroviral treatment (ART) free of pharmacological interactions[1,5,6] . This new patient, multi-pathological and polymedicated, demands a multidisciplinary approach, and the Hospital Pharmacy becomes a key agent in the task to prevent as much as possible any drug-related problem (DRP)[7].

In our HIV patient consultations, intervention strategies have been historically focused on patient information and the improvement in treatment adherence. Now, we must also face the challenge of an aging population and the management of concomitant treatments and their potential interactions, that might compromise the safety and/or efficacy of ARTs as well as of the rest of treatments[8,9].

The objective of this study is to understand, in real clinical practice, the frequency of potential pharmacological interactions in our patient cohort, and to identify those drugs most frequently involved, as well as their mechanisms and potential consequences. Obviously, this will help us to prevent them.

Methods

Design. A descriptive, retrospective study in a cohort of > 50-year-old patients on ART. The article has been prepared following the recommendations in the STROBE guidelines, available in: http://www.strobe-statement.org.

*Study setting, population and period of time. Hospital Universitario Virgen Macarena de Sevilla (*HUVM), a tertiary hospital with 800 beds and an assigned population as regional hospital of referral of 657,759 inhabitants.

Among other patients, 1,000 patients with HIV infection are seen per year at the external outpatient units, from Monday to Friday in the morning, and Mondays and Thursdays in the afternoon. There is one Pharmacy Technician and 1.5 Pharmacists in these units.

All > 50-year-old patients on ART were included, who had visited said units between January and December, 2014.

Sources of information. The Computer System by the Andalusian Public Health System, Diraya®, was used in order to identify home treatment, as support for the electronic clinical record and the application for outpatient dispensing by Farmatools®. In order to identify interactions, we used DRUGS.COM (www.drugs.com)[10], an on-line database of information on medications, feeding off four independent providers (WoltersKluwerHealth, American Society of Health-System Pharmacist, Cerner Multum and Micromedex), and the product specifications available at https://www.aemps.gob.es.

Study variables and data collection. The variables collected were: age, gender, home treatment, ART and potential pharmacological interactions. The classification by Drugs.com was used, selecting those Moderate and Severe. Finally we analyzed the number, type and mechanism of action of interactions, as well as their potential effects described in the sources of information.

For this study, those patients with five or more molecules as outpatient prescriptions were considered "polymedicated" patients.

Statistical analysis. A descriptive analysis using the statistical package SPSS Inc, Chicago, Illinois, version 18.0, with absolute and relative frequency used in order to describe the qualitative variables and the median, and the interquartile range for quantitative variables.

A univariate analysis was conducted in order to determine the association between the presence of potential pharmacological interactions and polymedication. For this objective, Square-chi test was used for the comparison of qualitative variables (Fisher's Exact test in case of non-parametric variables), with statistically significant differences when p-value was < 0.05.

Ethical considerations. The collection of retrospective data from the Clinical Record for research purposes was conducted by the investigators, who were also in charge of data anonymization. The Research Ethics Committee was requested to approve the study protocol, as well as the exemption for obtaining informed consent, as stated in current legislation (SAS Order 3470/2009 of December, 16th, and BOE 310, of December, 25th, 2009).

Results

The study included 242 patients; 189 (78%) were male. Their median age (interquartile range) was of 57.5 (54-62) years. The number of patients with home treatment was 148 (61.2%), and 117 were polymedicated (48.3% of the total number). There was a considerably higher frequency of pharmacological interactions in polymedicated patients vs. non-polymedicated patients: 81.2% vs. 18.8% (p < 0.005). Table 1 describes the ARTs used in our patient cohort.

Of the 243 potential interactions detected, 197 were considered moderate and 46 were severe, affecting 110 patients with the following distribution: 2 patients presented 7 potential interactions; 2 with 6; 3 with 5; 13 with 4; 18 with 3; 24 with 2, and 48 patients with one interaction. Thirty-four (34) patients (14% of the total number of patients) presented potentially severe interactions, with 46 interactions in total.

Table 2 describes the interactions detected according to severity, antiretroviral drug, home medication, therapeutic group, interaction mechanisms, and their potential effects.

The ARTs most frequently involved were boosted PIs (49.3%), followed by NNRTIs (38.3%). Considering severe interactions only, boosted PIs were responsible for 76% of cases. Regarding home treatment, most interactions involved psychiatric medication (28.4%), followed by cardiovascular drugs (25.5%).

Regarding severe interactions, statins were the group of drugs with higher involvement (24%), followed by inhaled corticosteroids (15%).

Regarding the consequences of these interactions, the outcome in 48% of them was an increase in the plasma concentration / effect of outpatient medication, in 24.3% there was a reduction, while in only 7.2% there was an impact on ART levels. In 23.4% of them, this consequence translated into

Table 1. Active antiretroviral agents (593) in our cohort (N = 242 patients)

Active ARTs		N (%)
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		321 (54.1)
Abacavir	ABV	29 (4.9)
Zidovudine	AZT	1 (0.2)
Emtricitabine	FTC	129 (21.7)
Lamivudine	3TC	34 (5.7)
Tenofovir	TFV	128 (21.6)
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		140 (23.6)
Efavirenz	EFV	76 (12.8)
Nevirapine	NVP	15 (2.5)
Etravirine	ETR	5 (0.9)
Rilpivirine	RPV	44 (7.4)
Protease Inhibitors (PIs)		112 (18.9)
Darunavir/ritonavir	DRV/r	81 (13.6)
Atazanavir/ritonavir	ATV/r	10 (1.7)
Fosamprenavir/ritonavir	FPV/r	5 (0.9)
Lopinavir/ritonavir	LPV/r	16 (2.7)
Fusion / entry Inhibitors (FIs)		8 (1.3)
Maraviroc	MVC	8 (1.3)
Integrase Inhibitors (INIs)		11 (1.9)
Raltegravir	RAL	10 (1.7)
Elvitegravir	EVG	1 (0.2)
Other		1 (0.2)
Cobicistat	COBI	1 (0.2)

*Ritonavir: 112 (18.9%).

Table 2. Description of the potential interactions detected according to severity, antiretroviral drug, concomitant medication and therapeutic class, interaction mechanisms and potential effects

ART	HOME TREATMENT	THERAPEUTIC CLASS	N	MECHANISM OF ACTION	POTENTIAL EFFECT
POTENTIALLY SEVERE INTERACTIONS					
ATV/r	Famotidine/ranitidine	Anti H2	2	Reduced absorption	Reduction of ART-PC
ATV/r	Atorvastatin/simvastatin	Statin	1	Inhibition of 3A4	Increase of D-PC
ATV/r	Dihydroergotamine	Antimigraine	1	Inhibition of 3A4	Increase of D-PC
ATV/r	Omeprazole	PPI	1	Reduced absorption	Reduction of ART-PC
DRV/r	Atorvastatin/simvastatin	Statin	10	Inhibition of 3A4	Increase of D-PC
DRV/r	Fluticasone/budesonide	Inhaled corticosteroid	7	Inhibition of 3A4	Increase of D-PC
DRV/r	Tamsulosin	Alpha-blocker	3	Inh. 3A4 and 2D6	Increase of D-PC
DRV/r	Salmeterol	Beta-blocker	2	Inhibition of 3A4	Increase of D-PC
DRV/r	Apixaban	DOAC	1	Inh. 3A4 and Pgp	Increase of D-PC
DRV/r	Phenobarbital	Antiepileptic: barbiturate	1	Induction of 3A4	Reduction of ART-PC
DRV/r	Ranolazine	Antanginal	1	Inhibition of 3A4	Increase of D-PC
DRV/r	Solifenacin	Urinary antispasmodic	1	Inhibition of 3A4	Increase of D-PC
DRV/r	Tamoxifen	Anti-estrogen	1	Inhibition of 2D6	Reduction of D-EF by inhibiting its bioactivation
LPV/r	Midazolam	Benzodiazepine	1	Inh. 3A4 and AE boosting	Increase of D-PC + QT
LPV/r	Quetiapine	Antipsychotic	1	Inh. 3A4 and AE boosting	Increase of D-PC + QT
LPV/r	Tamsulosin	Alpha-antagonist	1	Inh. 3A4 and 2D6	Increase of D-PC
RAL	Almagate	Antacid	1	Reduced absorption	Reduction of ART-PC
RPV	Citalopram/escitalopram	SSRIs	3	Boosted AEs	Increase of QT
RPV	Fenitoine	Antiepileptic: hydantoin	1	Induction of 3A4	Reduction of ART-PC
RPV	Omeprazole	PPI	1	Reduced absorption	Reduction of ART-PC
RPV	Ziprasidone	Antipsychotic	1	Boosted AEs	Increase of QT
TFV	Ibuprofen	NSAIDs	3	Boosted AEs	Nephrotoxicity
TFV	Methotrexate	Antimetabolite	1	Boosted AEs	Nephrotoxicity
POTENTIAL MODERATE INTERACTIONS					
ATV/r	Clorazepate/alprazolam	Benzodiazepine	3	Inhibition of 3A4	Increase of D-PC
DRV/r	Clorazepate/diazepam/ alprazolam	Benzodiazepine	20	Inhibition of 3A4	Increase of D-PC
DRV/r	Escitalopram/sertraline/ trazodone	Antidepressants: SSRIs	4	Inhibition of 3A4	Increase of D-PC
DRV/r	Glargine insulin / glulisine	Hipoglycemic: insulins	4	Unknown mechanism	Reduction of D-EF
DRV/r	Amlodipine	Calcium channel blocker	3	Inhibition of 3A4	Increase of D-PC
DRV/r	Levothyroxine	Thyroid hormone	3	Induction of UGT	Reduction of D-PC
DRV/r	Metfomin	Hipoglycemic: biguanide	3	Unknown mechanism	Reduction of D-EF
DRV/r	Losartan/valsartan	ARBs	2	Inhibiton of liver uptake	Increase of D-PC
DRV/r	Nasal Mometasone	Topical corticosteroids	2	Inhibition of 3A4	Increase of D-PC
DRV/r	Pravastatin	Statin	2	Unknown mechanism	Increase of D-PC
DRV/r	Risperidone / chlorpromazine	Antipsychotic	2	Inhibition of 2D6	Increase of D-PC
DRV/r	Sitagliptin	Hipoglycemic: gliptin	2	Unknown mechanism	Reduction of D-EF
DRV/r	Tramadol	Opioid	2	Inhibition of 2D6	Increase of D-PC
DRV/r	Venlafaxine /mirtazapine	Antideppresant: Other	2	Inh. 3A4 and 2D6	Increase of D-PC
DRV/r	Zolpidem	Hypnotic	2	Inhibition of 3A4	Increase of D-PC
EFV	Simvastatin/atorvastatin/ pravastatin	Statin	13	Induction of 3A4	Reduction of D-PC
EFV	Enalapril/ramipril	ACE Inhibitors	9	Boosted AEs	Hepatotoxicity
EFV	Clorazepate /diazepam	Benzodiazepine	6	Induction of 3A4	Reduction of D-PC
EFV	Cotrimoxazole	Sulphamides	4	Boosted AEs	Hepatotoxicity
EFV	Losartan	ARBs	3	Induction of 3A4	Reduction of D-PC
EFV	Amlodipine	Calcium cannel blocker	2	Induction of 3A4	Reduction of D-PC
EFV	Fenofibrate	Fibrates	2	Boosted AEs	Hepatotoxicity

Table 2 ***(cont.).*** Description of the potential interactions detected according to severity, antiretroviral drug, concomitant medication and therapeutic class, interaction mechanisms and potential effects

ART	HOME TREATMENT	THERAPEUTIC CLASS	N	MECHANISM OF ACTION	POTENTIAL EFFECT
POTENTIAL MODERATE INTERACTIONS					
EFV	Ibuprofen	NSAIDs	2	Boosted AEs	Hepatotoxicity
EFV	Tizanidine	Central Muscle Relaxant	1	Boosted AEs	Increase of QT
EFV	Sildenafil	Phosphodiesterase inhibitor	1	Induction of 3A4	Reduction of D-PC
ETR	Omeprazol/pantoprazol/ rabeprazol	PPIs	7	Inh. 2C9, 2C19	Increase of D-PC
ETR	Clorazepate /alprazolam	Benzodiazepine	5	Induction of 3A4	Reduction of D-PC
ETR	Atorvastatin	Statin	2	Induction of 3A4	Reduction of D-PC
ETR	Fluoxetine	Antidepressants: SSRIs	2	Inh. 2C9, 2C19	Increase of ART-PC
ETR	Ibuprofen	NSAIDs	2	Inh. 2C9, 2C19	Increase of D-PC
ETR	Zolpidem	Hypnotic	2	Induction of 3A4	Reduction of D-PC
FPV/r	Clorazepate/ alprazolam	Benzodiazepine	2	Inhibition of 3A4	Increase of D-PC
LPV/r	Clorazepate /alprazolam	Benzodiazepine	3	Inhibition of 3A4	Increase of D-PC
NVP	Atorvastatin/simvastatin	Statin	3	Induction of 3A4	Reduction of D-PC
RPV	Ranitidine	Anti H2	4	Reduction of. absorption	Reduction of ART-PC
RPV	Salbutamol/formoterol	Beta-blockers	2	Boosted AEs	Increase of QT
RPV	Hydroxyzine	Antihistaminics	1	Boosted AEs	Increase of QT
TFV	ASA at low doses	Salicylic Acid and derivates	8	Boosted AEs	Nephrotoxicity
TFV	Metformin	Hipoglycemic: biguanide	7	Inhibition of renal excretion	Increase of CP-both
TFV	Ranitidine	Anti H2	4	Inhibition of renal excretion	Increase of CP-both

PPIs: Proton Pump Inhibitors. SSRIs: Selective Serotonin Reuptake Inhibitors. NSAIDs: Non-steroid antiinflammatories. ARBs: Angiotensin II Receptor Blockers. ACE inhibitors: Angiotensin converting enzyme inhibitors. AEs: Adverse Effects. Inh: Inhibition of and the relevant subsequent P450 cytochrome (or the relevant enzyme). Ind: Induction of and the relevant subsequent P450 cytochrome (or the relevant enzyme). Increase of D-PC: Increase of the plasma concentration of the other drug. Reduction of D-PC: Reduction of the plasma concentration of the other drug. Increase of ART-PC: Increase of the plasma concentration of the antiretroviral. Reduction of ART-PC: Reduction of the plasma concentration of the antiretroviral. Increase of D-EF: Increase of the clinical efficacy of the other drug. Reduction of D-EF: Reduction of the clinical efficacy of the other drug. Increase of ART-EF: Increase of the clinical efficacy of the antiretroviral. Reduction of ART-EF: Reduction of the clinical efficacy of the antiretroviral. DOAC: Direct oral anticoagulant.

boosted adverse effects: we must highlight the risk of QT interval elevation and an increase in hypotensive effect with risk of falls.

Discussion

The median age (IQR) in our cohort of patients was 57.5 (54-62) years, and the majority were male (81.8%). These characteristics are similar to those described by Álvarez Martín *et al.*[11]. These authors included > 55-year-old patients, with a mean age of 60 years, and 78% of them were male. Over half of the patients were on some prescribed home treatment (61.2%), and in almost half of patients more than five different molecules were identified. In the study by Álvarez Martín *et al.*[11] almost 70% of patients had some associated medication.

We must highlight the high percentage of patients who presented some type of potentially moderate/severe interaction (44.6%), similar to the findings by Álvarez Martín *et al.*[11]. In over half of patients, more than one interaction was identified, and there were even patients with seven simultaneous potential interactions.

In the review by Manzardo C *et al.*[6], boosted PIs were the ARTs more frequently associated with severe interactions. Equally, Molas E *et al.*[13] revealed that PIs were the group of drugs with higher interactions, with a 47% rate which is similar to the one in our cohort. And at the same time, in the study by Yiu P *et al.*[12] , PIs were again the agents with more interactions present, both in young (44%) and in elderly patients (42%). In this study, these were followed by Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs). In our case, however, there was a wide superiority of NNRTIs vs. NRTIs, 38.3 vs. 10.3% respectively.

Regarding outpatient treatments, outcomes were similar to ours both in the studies by Martín[11] and in the study by Marzolini C[14], given that psychiatric and cardiovascular medication presented the higher percentage of interactions. And this is also comparable with the study by Tseng A[15] where cardiovascular medication occupied the first place (37%).

We have detected a high frequency of interactions classified as severe in Drugs (18%); this rate is superior to the one described in other studies, and we must highlight the involvement of statins.

One of the main limitations in our study could be its retrospective nature; but given the fact that it is merely descriptive, it is not considered very relevant.

Finally, we must highlight that this knowledge of the drugs involved, as well as of the mechanisms of interactions and their potential effects, will allow us to design strategies targeted to an early detection of patient-medication groups at higher risk, and ultimately to an improvement in health outcomes.

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Conflicts of interest

No conflicts of interest declared.

Contribution to scientific literature

This article shows the clinical reality in our patients, and analyzes in detail an area of growing interest with limited scientific production. Given the aging in the HIV population, fortunately this is a matter that presents particular relevance: a better knowledge of pharmacological interactions and their potential effects will allow us to select and classify our patients / higher-risk medication, and anticipate strategies targeted to improving health outcomes. The importance of the Pharmacist role is also highlighted; through pharmacotherapeutical follow-up and due to their closeness and access to patients, they will play a key role from the Pharmacy Outpatient Units, beyond mere dispensing.

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