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ORIGINAL ARTICLE

Polypharmacy among HIV infected people aged 50 years or older

Polifarmacia en pacientes mayores de 50 años con infección por el VIH.

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Abstract

Introduction:

Although HAART cannot eradicate HIV, it suppresses viral replication, resulting in a progressive reduction in HIV-related morbidity and mortality. The increase in life expectancy for HIV-infected patients has turned this disease into a chronic disease and, therefore, to the appearance of comorbidities. At the same time there is an increase in the use of concomitant medication, making HIV-infected patient a polymedicated patient.

Objective:

To determine the degree of polypharmacy and to describe clinically relevant drug interactions, as well as the comorbidities and adherence to HAART in HIV + patients over 50 years.

Methods:

Observational, transversal study. Patients ≥50 years on HAART ambulatory were included. The variables were collected: aged, sex, VL, CD4, comorbidities, ARV, concomitant medication, herbal products and adherence. Patients who did not sign informed consent were excluded.

Results:

Were included 154 patients ≥50 years on HAART. The presence of polypharmacy, defined as the use of 5 or more medications including HAART, was 40.3%. 73.4% of the patients had concomitant medication: lipid-lowering agents (33.8%), anxiolytics / sedatives (28.6%), proton-pump inhibitors (26.0%) antihypertensive agents (23.4%). 102 relevant interactions were recorded, finding statistically significant differences in relation to the presence of polypharmacy and pharmacologic drugs classes (p <0.001).

Conclusion:

The prevalence of polypharmacy among HIV+ patients ≥50 years is high. Comorbidities, interactions and drugs associated were similar to those described in the literature. It is necessary to establish priorities in relation to drug interactions with polypharmacy and a correct approach to the pathologies that may develop.

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Conflicts of interest:
No conflict of interest

Resumen

Introducción:

El HAART, si bien no puede erradicar la infección por el VIH, mantiene suprimida la replicación viral obteniendo una progresiva reducción de la morbimortalidad. El aumento de la esperanza de vida ha convertido a esta enfermedad en una patología crónica y por tanto, a la aparición de comorbilidades. Paralelamente, se produce un incremento en el uso de medicamentos que califican al paciente VIH como polimedicado.

Objetivos:

Determinar el grado de polifarmacia, describir las interacciones relevantes, así como conocer las comorbilidades y la adherencia al HAART en pacientes VIH+ ≥50 años.

Métodos:

Estudio descriptivo, transversal. Se incluyeron pacientes ≥50 años VIH + con terapia HAART ambulatoria. Se recogieron las variables: edad, sexo, carga viral, CD4, comorbilidades, tratamiento antirretroviral, medicación concomitante, productos de herboristería y adherencia.

Resultados:

Se incluyeron 154 pacientes ≥50 años con HAART. La polifarmacia, definida como la presencia de 5 o más principios activos incluido el HAART, se presentaron en el 40.3% de los pacientes. El 73.4% tenía medicación concomitante: hipolipemiantes (33.8%), ansiolíticos/sedantes (28.6%), inhibidores de la bomba de protones (26,0%), antihipertensivos (23.4%). Se registraron 102 interacciones relevantes encontrándose diferencias estadísticamente significativas en relación a la presencia de polifarmacia y al grupo farmacológico antirretroviral (p<0,001).

Conclusiones:

Existe una alta prevalencia de polifarmacia en pacientes VIH+ ≥50 años. Las comorbilidades, las interacciones identificadas y la medicación concomitante fueron similares a las descritas en la literatura. Es necesario establecer prioridades en relación a las interacciones farmacológicas con la polifarmacia y un correcto abordaje de las patologías que se puedan desarrollar.

Remark

1)Why was this study conducted?

The study was carried out due to the high rate of HIV patients over 50 who came to the pharmacy to pick up the medication and for whom in many cases the concomitant treatment they were currently taking had not been updated

2) What were the most relevant results of the study?

The use of integrase inhibitors may be a good alternative for those polymedicated patients.

3) What do these results contribute?

As the number of drugs used increases, the problems related to medication increase, leading to a lower adherence to HAART, as well as an increase in the number of potential pharmacological interactions, so a more exhaustive follow-up should be carried out in this group of patients

Introduction

The number of patients who are over 50 years old and are infected with HIV has increased; this is linked to an increase in the survival of patients undergoing antiretroviral therapy (HAART) [1]. It is estimated that almost half of the patients with HIV and 16.4% of new HIV diagnoses were over 50 years old in Spain in 2017 [2]

The same recommendations regarding the management of HIV infection in adults and adolescents also apply to older adults, but certain important problems in this age group must be taken into account, such as polypharmacy and the comorbidities associated with ageing [3].

Sexual exposure is the most common form of transmission in this group, around 40% in the case of heterosexual transmission. The use of injected drugs is an important risk factor but it is less common [4]. These patients are not perceived as a group at risk of contracting HIV and frequently it is less likely that they carry out diagnostic tests [1], therefore, a delay in diagnosis is more common, together with the consequent increase in morbidity and mortality that late diagnosis entails. In their favour, older patients with an HIV infection tend to be more adherent than younger patients, with more than 95% adherence [5,6].

There are many definitions of polypharmacy; these also differ if we pay attention to quality or quantity criteria. The WHO defines polypharmacy as ``the simultaneous administration of various medications or the administration of an excessive quantity of medications´´[7]. The quantitative criteria only define the number of drugs used for at least 90 days, 5 or more drugs being the most used value [8], without determining the suitability of the therapy. Regarding the qualitative criteria, polypharmacy is defined as the consumption of more medicines than clinically indicated. In a systematic review 3 possible situations are recognised: appropriate polymedication (the patient takes a lot of medications but all of them are medically indicated), inappropriate polymedication (more medication is taken than clinically needed) and pseudo-polymedication (more medication is registered on the pharmacotherapeutic record than what the patient is really taking)[9]. Despite being a public health problem there are few studies published about polypharmacy in older patients with an HIV infection; together with drug interactions, this issue is a specific challenge for this group.

A thorough review of all medication and supplements taken is an important part of the pharmaceutical care of these patients. In the study carried out by Greene et al. [10], of 89 patients infected with HIV over 60 years old, the median number of drugs per patient was 13, and 70% of the patients had at least one possible drug-drug interaction of category D (consider modification) compared with 39% of patients not infected with HIV of the same age and sex.

HAART has increased the survival rate of people with an HIV diagnosis. As the number of deaths associated with AIDS and opportunistic infections decreases, the comorbidities associated with age have become more prevalent (cardiovascular, metabolic, hepatic and bone diseases and malignant disease)[11]. This is partly due to chronic inflammation, immune activation and the immunosenescence associated with HIV[12].

The ageing of the HIV+ population is a growing reality that generates uncertainty and an additional difficulty in the care approach of these particularly fragile patients. It is necessary to further the knowledge of the most prevalent diseases and the pharmacological therapies that are used if we want to offer the best possible treatment to these patients.

The aim of our study was to determine the level of polypharmacy and the number of clinically relevant interactions in HIV+ patients of 50 years or more, in active antiretroviral treatment. Additionally we hope to quantify the comorbidities, the level of adherence, and establish a possible connection with polypharmacy.

Material and Methods

Observational, cross-sectional study performed in the area of pharmaceutical dispensation and assistance to outpatients of the Pharmacy Service.

The study was carried out during a period of 4 months (December 2017 to March 2018). We included patients with an HIV+ diagnosis aged 50 years or over that have been coming to collect their antiretroviral medication for at least 1 year (minimum diagnosis time) and that authorised their inclusion in the study with informed consent. Patients with physical or mental disabilities, those that did not sign their informed consent or those that do not personally come to collect their medication were excluded from the study. The Medical Research Ethics Committee of our hospital approved the protocol for the data collection.

The clinical data (viral load (VL), the level of lymphocytes CD4+, HBV and/or HCV co-infection) was obtained from the laboratory informatics unit. The information related to treatment (current HAART, time of treatment (<5 years or >5 years), the discontinuing of HAART in months, concomitant drugs, dosage including HAART) and to the type of comorbidities was obtained from the electronic health record (Medora®), from the electronic prescription programme for outpatients (Farmatools®) and via direct structured interview with the patient. The interview was conducted taking into account the objectives of this study, so the questions are aimed at achieving these objectives. The interview consists of three main blocks: demographic and clinical data of the patient, data related to the treatment and habits of the patient's life and finally adherence data. The drugs were classified by the ATC (Anatomical Therapeutic Chemical classification) system. The comorbidities were quantified using the Charlson index (CCI) adjusted by age [13]. This index consists of 19 pathologies assessed from 1 to 6, with a total score that varies between 0 and 37 points, from 50 years old onwards one point is added for each decade. All the participants were assigned an initial score of 1 (according to the CCI for an added age point). Patients with dementia were not included in the study and therefore this disease did not count. The values obtained were classified in 3 categories: 1-3, 4-8 and ≥9.

The patients were classified according to the number of drugs prescribed and polypharmacy was defined as the use of 5 or more medications of persistent use (in treatment for at least 90 days) [14], HAART was considered as one medication. For the combinations of medication other than retroviral drugs the pharmacological properties were considered and were counted individually. One-off prescription medication was included (only if certain conditions were produced) if the patient had taken the medication regularly in the previous two weeks, defining regularly as 4 or more days per week. Drugs for acute conditions, antibiotics, intravenous drugs, topical medication, eye drops and enteral nutrition were excluded [15].

Herbal products were not included in the definition of polypharmacy.

To determine the number and the level of interaction between HAART and non-HAART, an online database of antiretroviral interactions from the University of Liverpool [16)] was used. For concomitant medication not categorised in said database we resorted to the online database Lexi-Interact [17], and for herbal products the online database Drug Interactions Checker [18] was used. The interactions were classified as contraindication, potential interaction, weak interaction and no interaction. Subsequently the contraindicated interactions and the potential interactions were analysed and were ranked b according to the pharmokinetic (with increase or decrease of dose) or pharmodynamic type.

The information about lifestyle habits (smoking, alcohol consumption, substance abuse and consumption of herbal products (including vitamins, minerals and other supplements)) was obtained via a direct structured interview with the patient. The habit of smoking was classified as a daily smoker, occasional smoker, ex-smoker or had never smoked. Alcohol consumption and substance abuse were classified as non-consumption, occasional consumption or daily consumption.

The data regarding treatment compliance was obtained via indirect methods: the validated SMAQ questionnaire and from the dispensation records of the last 6 months [19]. The SMAQ questionnaire consists of 6 questions with closed answers (YES/NO), the questionnaire is dichotomous, and any answer in a non-adherent sense is considered non-adherent. The dispensation records of the last 6 months were obtained from the programme Farmatools®. The following formula was used to calculate the level of adherence according to these records:

$$\%\ Adherence = \frac{number\ of\ units\ dispensed - number\ of\ units\ returned}{number\ of\ units\ prescribed} \times 100$$

Table 1. Sociodemographic characteristics, comorbidities, charlson comorbidity index and life habits of the patients studied according to the presence of polypharmacy. All results are expressed as percentages

	Total patients (n=154) n (%)	Pacients with polypharmacy (n=62) n (%)
Sex		
Female	31.0 (20.1)	17 (11.0)
Age, years (range)	56.3 (50.0-73.0)	57.6 (50.0-73.0)
Comorbidities		
Age range (years)	**median (range)**	**median (range)**
50-54 (n= 68)	3.5 (0.0-8.0)	5.2 (1-8)
55-59 (n=55)	4.0 (0.0-11.0)	6.1 (2-11)
60-64 (n=17)	4.8 (0.0-7.0)	7.3 (6-9)
65-69 (n=7)	4.3 (1.0-11.0)	11.0 (11)
≥70(n=7)	3.7 (1.0-5.0)	4.2 (3-5)
Comorbid conditions (Weights)	n (%)	n (%)
Myocardial infarction (1)	6 (3.9)	6 (9.7)
Peripheral vascular disease (1)	8 (5.2)	7 (11.3)
Cerebrovascular disease (1)	5 (3.2)	2 (3.2)
Chronic pulmonary disease (1)	10 (6.5)	9 (14.5)
Connective tissue disease (1)	2 (1.3)	2 (3.2)
Peptic ulcer disease (1)	11 (7.1)	8 (12.9)
Mild liver disease (1)	33 (21.4)	15 (24.2)
Diabetes (1)	22 (14.3)	18 (29.1)
Diabetes with chronic complication(2)	1 (0.7)	1 (1.6)
Renal disease (moderate to severe) (2)	8 (5.2)	7 (11.3)
Cancer (2)	8 (5.2)	4 (6.5)
Malignant lymphoma (2)	4 (2.6)	1 (1.6)
Moderate or severe liver disease (3)	10 (6.5)	6 (9.7)
Charlson Comorbidity Index (CCI)		
1-3	61 (39.6)	18 (29.0)
4-8	49 (31.8)	21 (33.9)
≥9	44 (28.6)	23 (37.1)
Habits		
Tobacco consumption	76 (49.4)	24 (38.7)
Daily smoker	68 (44.2)	23 (37.1)
Occasional smoker	7 (4.6)	1 (1.6)
Never smoker	20 (13.0)	8 (12.9)
Ex-smoker	59 (38.4)	30 (48.4)
Alcohol consumption		
Daily consumption	33 (21.4)	11 (17.7)
Occasional consumption	66 (42.9)	24 (38.7)
Non-consumption	55 (35.7)	27 (43.6)
Substance abuse		
Daily consumption	9 (5.8)	2 (3.2)
Occasional consumption	9 (5.8)	1 (1.6)
Non-consumption	136 (88.3)	59 (95.2)

An adherent patient was defined as one which simultaneously fulfilled a percentage of adherence ≥95% and a positive SMAQ questionnaire.

For the analysis of the data the SPSS® statistics software package was used. The continuous quantitative variables were defined as average and standard deviation, and the categorical variables as a percentage (%). Using Pearson's Chi-Squared test the association of the qualitative variables was analysed. The comparisons of the quantitative values were carried out using Student's T test or the one-way ANOVA test for independent samples according to the case. The values of p <0.05 were considered statistically significant.

Results

The interview was proposed to 225 patients, of which 54 patients refused their inclusion in the study, 12 did not come personally to pick up their medication, 3 presented cognitive difficulties to understand the study, and eventually 2 didn´t sign informed consent. Lastly among the 154 patients who had participated in the study, 20.1% (n=31) were women with a mean age of 56.3 (50-73). The prevalence of polypharmacy was 40.3% (n= 62). Detailed information is included in Table 1.

The sociodemographic characteristics of the included patients (n= 154) as well as the characteristics and distribution of comorbidities are described in Table 1. These data are also shown in patients identified as treated with polypharmacy. Statistical significance was only found for polymedicated patients based on age (p= 0.004) and comorbidity (p <0.001).

VL was undetectable in 90.9% of patients (n= 140), and only the remaining 9.1% (n= 14) had VL greater than 20 copies/mL (21-2,683). The average level of CD4 lymphocyte was 723.92 ±343.57 cells/µL. 68.2% (n= 105) had a CD4 cell count greater than or equal to 500 cells/µL (mean 894.25 cells/µL); 28.6% (n= 44) CD4 count between 200 and 499 cells/µL (average 385.23 cells/µL) and finally 3.3% (n= 5) CD4 count less than 200 cells/µL (average 127.60 cells/µL). There were no statistically significant differences in the proportion of patients with VL >20 copies/mL or CD4 count among those patients with or without polypharmacy.

In relation to HIV infection, 92.9% (n = 143) received HAART for more than 5 years. 93.6% (n= 131) submitted to triple therapy regimen based on 2 nucleoside analogue reverse transcriptase inhibitors (NRTIs) plus a third drug, the majority of which was emtricitabine/tenofovir (58.8%, n= 77) followed by abacavir / lamivudine (40.5%, n= 53) and finally zidovudine / lamivudine (0.8%, n= 1). The third drug was a non-nucleoside reverse transcription inhibitor (NNRTI) in 43.5% (n= 57) of patients, 42.8% (n= 56) an integration inhibitor (INSTI) and 13.7% (n = 18) a protease inhibitor (PI/p).

The 6.4% (n= 10) received another triple therapy regimen; 5.2% (n= 8) dual therapy; 2.0% (n= 3) monotherapy; and only 0.7% (n= 1) for quadruple therapy and quintuple therapy.

The average number of HIV medications was 2.1 (1-12). Almost half of the patients had a smoking habit (49.4%) with an average consumption of 5.1 ±3.0 tobacco packs per week; and only 11.7% abuse of some substance, mostly cannabis (88.9%). No statistically significant differences associated with presence of polypharmacy were apparent by any of the three variables.

The description of non-hiv medicines is detailed in Table 2. 73.4% (n= 113) of the patients received some concomitant medication. The most commonly used medicines were hypolipidemic agents (33.8%), followed by the anxiolytic / sedative (28.6%) and proton pump inhibitors (26.0%). 66.4% (n= 75) of the patients with any non-HIV medicines, took between 1 and 4 medicines, and the remaining 33.6% took 5 or more medicines.

Table 2. Prevalence of use of concomitant medications by pharmacological classes

Non-HIV medications	n (%)
Hypolipidemic agents	52 (33.8)
Anxiolytic/Sedative	44 (28.5)
Proton pump inhibitors	40 (26.0)
Antihypertensive agents	36 (23.4)
Diuretics	20 (13.0)
Antidiabetic drugs	19 (12.3)
Respiratory therapy	16 (10.4)
Antiplatelet agents	13 (8.4)
Opiods	10 (6.5)
Antipsychotics	9 (5.8)
Calcium and derivatives	9 (5.8)
Benign prostatic hypertrophy	9 (5.8)
NSAIDs	8 (5.2)
Cardiac therapy	7 (4.5)
Anticonvulsants	7 (4.5)
Antibacterial drugs	7 (4.5)
Anti-gout agents	7 (4.5)
Antihistamines	3 (2.0)
HVC antivirals	3 (2.0)
Corticoids	3 (2.0)
Oral iron	3 (2.0)
Other anti-ulcer drugs	3 (2.0)
HVB antivirals	2 (1.3)
Anticoagulants	1 (0.7)

n=154

Table 3. Statistical analysis in relation to the antiretroviral regimen and the presence of pharmacological interactions.

Antirretrovirals clases	Drug interactions	OR IC:95%
Protease inhibitors	8.82	4.07-19.14
Non-nucleoside reverse transcriptase inhibitors	2.65	1.40-5.02
Integrase inhibitors	0.72	0.35-1.48
Nucleoside reverse transcriptase inhibitors	0.10	0.04-0.25

The median number of non-HIV medications was 3.8 (1-17), in the case of patients with polypharmacy it was 6.0 (3-17). 57.8% of the patients took some herbal product.

Were recorded 102 relevant interactions between HAART and non-antiretroviral drugs in a total of 52 patients (96.1% potential interactions and 3.9% contraindicated interactions); and 32 weak interactions in a total of 27 patients. The contraindicated interactions corresponded to 2 patients with atazanavir-esomeprazole treatment, 1 patient with rilpirivin-omeprazole and another patient with quetiapine-lopinavir / ritonavir.

Interactions pharmacokinetic were the 84.3% (n = 86), of which 55.8% would imply a dose reduction. NNRTIs was the mainly antiretroviral involved with 36.4% of the potential interactions, followed by PI with 34.5%.

The potential interactions detected with HAART was mainly observed with central nervous system drugs (23.0%), antihypertensives (13.0%), calcium salts (11.5%), antidiabetics (6.9%), bronchodilators (6.9%) and lipid lowering agents (5.8%).

Only two potential interactions HAART-herbal products were recorded in two patients corresponding to the use of preparations with magnesium salts-dolutegravir.

In relation to cannabis use, potential interactions were recorded in three patients, all of them being treated with a regimen that included PI and presenting detectable VL.

Regarding the HAART used, Table 3 shows the influence of drug classes on the appearance of interactions. The presence of PIs and NNRTs is a significant risk factor (p <0.001).

Statistical analysis showed significant differences in the appearance of relevant interactions (contraindicated and potential) between patients with or without polypharmacy (p <0.001)

The study of adherence to HAART showed that 50.7% (n = 78) of the patients met the adherence criteria (simultaneously a percentage of pharmacy dispensing records (RD) ≥95% and a positive SMAQ questionnaire). Of the total number of patients, 53.3% (n = 82) presented a positive SMAQ questionnaire and 68.8% (n = 106) a ≥95% pharmacy dispensing record. The results of both methods differed in 36.4% (n= 56) of the patients. When the impact of the polypharmacy was analyzed, 41.9% (n= 26) of the patients were adherent, 40.3% (n= 25) presented a positive SMAQ and finally 64.5% (n= 40) a dispensing record ≥95%. There were statistically significant differences in the adherence with each methods between patients with or without polypharmacy (p <0.01)

Table 4 shows the results of adherence to HAART according to the polypharmacy and the age of the patients.

Table 4. Compliance to HAART according to SMAQ questionnaire and pharmacy dispensing records of the last six months.

	Adhesion Measurement Method					
	Total patients			Patients with polypharmacy		
	RD95%+SMAQ	RD95%	SMAQ	RD95%+ SMAQ	RD95%	SMAQ
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Age (years)						
50-54	33 (48.5)	47 (69.1)	38 (55.9)	15 (65.2)	19 (82.6)	16 (69.6)
55-59	27 (41.8)	34 (61.8)	27 (49.1)	4 (40.0%)	8 (80.0)	2 (20.0)
60-64	9 (52.9)	13 (76.5)	8 (47.1)	4 (50.0)	7 (87.5)	4 (50.0)
65-69	7 (100.0)	7 (100.0)	7 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)
≥70	2 (28.6)	5 (71.4)	2 (28.6)	2 (28.6)	5 (71.4)	2 (28.6)

Discussion

The results of our work show a high prevalence of polypharmacy in the HIV infected population aged over 50. On the other hand, we found that the percentage of patients with that age was around 50%. These discoveries are concordant with the data that comes from extensive epidemiological studies [20]. The importance that elderly patients are acquiring in the group of patients is becoming clear, together with the need to study the implications that the presence of numerous drugs can produce in this group.

The prevalence of polypharmacy in our study (40.3% for both sexes) is slightly lower than that which was described by Gimeno Gracia *et al.* [21] (43.8% and 47.2% for men and women respectively) in a group very similar to ours. It is possible that these differences reflect the years that have passed between that study (2015) and ours, and the growing trend to avoid medication that is not strictly necessary. The groups of non-antiretroviral drugs most prescribed in our study are similar to cohorts of patients of other previous studies [10,22] , although there is a higher consumption of antiulcer drugs. This fact could be relevant since this group of drugs is the object of potential interactions with medical relevancy.

Regarding the presence of other pathologies, 94.8% of the patients in the study presented some comorbidity. Notable comorbidities are musculoskeletal and of the conjunctive tissue; endocrine, nutritional and metabolic; infectious and of the circulatory system. This data is similar to the data from the cohort VACH [23]. Against what was expected [24,25], no statistically significant differences were found between the presence of comorbidities in the older patient (age >50 years old) and the elderly patient (age >65 years old) (p= 0.73). In order to interpret this fact we must consider that it is possible that our patient sample was insufficient to bring these differences to light, together with the fact that factors such as the time until diagnosis, the duration of HAART or the number of CD4 can influence the presence of comorbidities [26].

In our study all the patients had an initial CCI value of 1, the life expectancy at 10 years was above 90% in 30.5% of the patients (n= 47) and equal to or less than 0.01% in 53.3% of patients (n= 82). However, said rate presents the limitation that after its publication, the mortality in patients with HIV has dropped considerably with the appearance of HAART [27], it is estimated that by the year 2030 almost three quarters of the people that live with HIV will be aged 50 or more [28]. In our study, the presence of polypharmacy was linked with more elevated values of CCI (p <0.05).

The risk of interaction obtained (46%) is a little above that which was observed in other publications in which said risk is around 35% [22,29)] . Our work investigated the presence of non-antiretroviral medication combining a methodology based on the dispensation informatics records, together with the direct interview with the patient. In this way, it was possible to have access to the presence of self-medication, between which we found the use of antiulcer drugs and natural medicine products. We therefore extended the number of drugs present and consequently the number of possible pharmacological interactions was extended.

The groups of non-antiretroviral medication implied in the potential interactions are similar to those described in the literature [22,29]. The contraindicated interactions of our study corresponded to the concomitant treatment atazanavir-esomeprazole, rilpirivine-omeprazole and quetiapine-lopinavir/ ritonavir.

The concomitant use of drug combinations that include atazanavir or rilpirivine and omeprazole produces a reduction in their concentration due to the fact that the increase of gastric pH caused by omeprazole reduces their absorption therefore boosting the risk of a virological failure [10]. On the other hand quetiapine is metabolised through the CYP3A4 therefore its co administration with a cytochrome inhibitor like lopinavir causes an increase in its concentration which increases the risk of QT interval prolongation [10].

In the Cordova *et al*[29] study, it is shown that the regimens that include PI or NNRTIs produce a greater number of interactions without observing significant differences between both regimens. Our results identified a greater risk of interaction with regimens that included a PI followed by the regimens that contained NNRTIs. This data suggests that the use of INI would be a safer alternative in polymedicated patients.

The compliance with the treatment is another element that can be negatively influenced by polypharmacy, with the importance that can stem from it.

The study demonstrates a greater adherence in patients without the presence of polypharmacy and in the group aged between 65-69 years old. Our work did not show a significant relationship between the virological results of the patients and polypharmacy. It is possible that the low number of patients and the methodology used to determine adherence can contribute to limiting the ability of establishing this relationship.

The patients with detectable VL were 9.1% (n=14), of which 71.4% (n=10) were non-adherent and therefore the risk of having a detectable VL in a non-adherent patient was 12.5% (p <0.5). The SMAQ questionnaire is restrictive as it classes a patient as non-adherent with one negative answer which can cause a lower percentage of adherent patients than the dispensation record; however the simplicity of said questionnaire facilitates its use. The dispensation record shows a good correlation with the virological results [30], in addition if the dispensation is centralised it is simple to obtain, but it does not imply a correct compliance of the patient. The discrepancy between both methods was 36.4% (n= 56). This brings the underestimation of compliance of the SMAQ questionnaire to light without adding substantially predictive information, the data of the dispensation record and the patient's viral load were better indicators. This data is contrary to that presented by Codina *et al.*[31] in which it was concluded that both methods overestimated adherence, although it is ensured that the patients classified as non-compliant really were non-compliant.

Our study valued the impact that polypharmacy has on HAART, but it did not investigate the effect of polypharmacy on HAART. There are experiments that show its importance [32], although we consider that this surpassed the objectives of the current work and could possibly be a motive for future investigations.

It is possible that if a greater sample had been available, the statistical power would have brought other results to light. Nevertheless the difficulty of accessing these patients and this type of information must be taken into account.

The choice of methodology used in our study, both to determine adherence, to define comorbidity or even for the very definition of polypharmacy can be questioned, as can be demonstrated by the fact that they are a frequent object of reviews and investigations. Despite this, we believe that our choice is justified, and even if other criteria had been chosen, our discoveries would not have been notably affected.

Conclusions

The comorbidities associated with patients with HIV over 50 years old and the prevalence of polypharmacy is very high. As the number of drugs used increases, the number of possible problems related with medication also increases, these include a negative impact on adherence to HAART, and an increase in the number of potential pharmacological interactions which are more frequent in patients that are being treated with PIs or NNRTIs. This data allows us to establish that polypharmacy must be an object of priority in the assistance of this group of patients and our efforts must be directed not only to establishing an adequate control of HIV but also to carrying out an appropriate pharmacological approach of the pathologies that can develop with time.

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