Evaluation of drug interactions and their impact on virological failure of people living with HIV/AIDS over 50 years of age

Avaliação das interações medicamentosas e seu impacto no fracasso virológico de pessoas vivendo com HIV/AIDS acima de 50 anos de idade

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ABSTRACT

The discovery of the antiretroviral therapy (ART) increased life expectancy of people living with HIV (PLHIV). This chronic condition was associated with other diseases with a higher risk of multiple drug use and drug interactions. Drug interactions can cause therapy failures and side effects. This cross-sectional study was carried out in three specialized clinics located in the northwestern of the state of São Paulo from September to December 2019, and evaluated the potential drug interactions in PLHIV and its impact on virological failure. PLHIV aged 50 years or older were included, using ART and other drugs for more than one year and viral load tests in the last 6 months. The data were obtained through a structured questionnaire and medical records. The interactions were analyzed by the Liverpool drug interaction database. The virological failure was defined as two exams of viral loads above 200 copies/ml. We performed a descriptive analysis of the results. Among the 113 people included in the study, 43.36% acquired the virus after

the age of 50 and 61.95% reported had never stopped using ART. There were comorbidities (89.38%), the main ones: arterial hypertension (47.79%), diabetes (20.35%) and depression (17.70%). The drug interactions appeared in 74.34% of the respondents and 7.08% presented contraindicated interactions. The drugs involving the central nervous system were responsible for most interactions (47.58%), followed by antihypertensive drugs, hypoglycemic drugs and statins. Protease inhibitors and non-nucleoside reverse transcriptase inhibitors showed a higher number of interactions. Only three individuals (2.65%) showed virological failure, two of which presented adherence failure. Drug interactions were very prevalent among individuals with HIV/AIDS over 50 years of age and these interactions have the potential to change mainly the comedication concentration and have no significant impact on virological failure.

Keywords: HIV infections, aging, anti-retroviral agents, polypharmacy, drug interactions.

RESUMO

A descoberta da terapia anti-retroviral (ART) aumentou a expectativa de vida das pessoas vivendo com HIV (PLHIV). Esta condição crônica foi associada a outras doenças com maior risco de uso múltiplo de drogas e interações medicamentosas. As interações medicamentosas podem causar falhas terapêuticas e efeitos colaterais. Este estudo transversal foi realizado em três clínicas especializadas localizadas no noroeste do estado de São Paulo de setembro a dezembro de 2019, e avaliou as potenciais interações medicamentosas na PVHA e seu impacto sobre as falhas virológicas. Foram incluídas as PLHIV com 50 anos ou mais, usando ART e outras drogas por mais de um ano e testes de carga viral nos últimos 6 meses. Os dados foram obtidos através de um questionário estruturado e registros médicos. As interações foram analisadas pelo banco de dados de interação de medicamentos de Liverpool. A falha virológica foi definida como dois exames de cargas virais acima de 200 cópias/ml. Realizamos uma análise descritiva dos resultados. Dentre as 113 pessoas incluídas no estudo, 43,36% adquiriram o vírus após a idade de 50 anos e 61,95% relatadas nunca haviam parado de usar ART. Houve comorbidades (89,38%), as principais: hipertensão arterial (47,79%), diabetes (20,35%) e depressão (17,70%). As interações medicamentosas apareceram em 74,34% dos entrevistados e 7,08% apresentaram interações contraindicadas. As drogas envolvendo o sistema nervoso central foram responsáveis pela maioria das interações (47,58%), seguidas por drogas anti-hipertensivas, drogas hipoglicêmicas e estatinas. Os inibidores de protease e os inibidores de transcriptase reversa não-nucleosídeos apresentaram um número maior de interações. Apenas três indivíduos (2,65%) apresentaram falha virológica, dois dos quais apresentaram falha de aderência. As interações medicamentosas foram muito prevalentes entre indivíduos com HIV/AIDS acima de 50 anos de idade e essas interações têm o potencial de mudar principalmente a concentração de comedicação e não têm impacto significativo na falha virológica.

Palavras-chave: Infecções por HIV, envelhecimento, agentes anti-retrovirais, polifarmácia, interações medicamentosas.

1 INTRODUCTION

With the discovery of the highly active antiretroviral therapy (ART) against HIV there was a reduction in mortality rates and an increase in the life expectancy of these individuals approaching a person without virus infection[1,2].

According to the United Nations Joint Programme on HIV/Aids (UNAIDS), in 2019 about 38 million people were living with HIV, and 25.4 million of them had access to antiretroviral therapy, compared to 6.4 million in 2009[3].

In Brazil, from 1980 to June 2019, 966.058 cases of AIDS were diagnosed. In the last ten years, an increase in the number of cases of men in the age group over 60 years were observed[4]. The country offers state-of-the-art antiretroviral therapy, composed primarily of Lamivudine, Tenofovir and Dolutegravir, widely disseminated to the HIV population through a public, universal and free system[5].

HIV treatment has improved substantially since the introduction of the ART and it has transformed it into a chronic condition consequently associated with other diseases and increased risk of multiple drug use[6,7,8].

It is emphasized that, mainly after the development of drugs that improve sexual performance such as the use of prostheses for erectile dysfunction by men and hormone replacement by women, the elderly have become increasingly sexually active. In addition, older individuals are less likely to have safe sex[9,10]. The higher prevalence of comorbidities, the use of multiple drugs, and drug interactions in this population require a multidisciplinary approach, besides, it is necessary to develop public health policies involving prevention guidelines adapted to the elderly[11, 12].

The consequences on aging caused by the use of drugs in HIV-infected individuals are not well known, as well as the potential for drug interactions with ART and other co-administered drugs and the impact of these factors on the tolerability of therapy and the virologic response[13,14]. The fact is that pharmacokinetic interactions between ART and other concomitant medicines are common and may lead to an increase or a decrease in drug exposure, reducing the effectiveness of said therapy or increasing its toxicity[15,16]. Studies in the Netherlands, the United States and Kenya showed a potential for clinically significant interactions between 14 - 41% of patients[16]. Therefore, the prevention, the identification, and the management of drug interactions are crucial for patient care[17].

The aim of this study was to evaluate the potential drug interactions in people living with HIV/AIDS over 50 years of age and to reveal the impact of these interactions on virological failure.

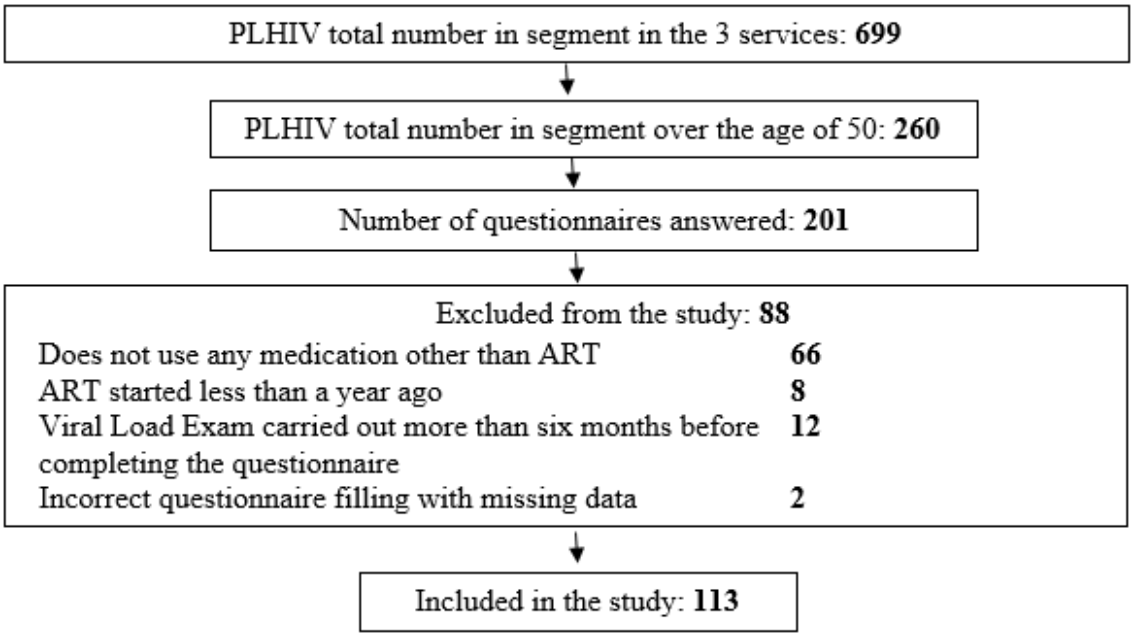
2 MATERIAL AND METHODOS

2.1 STUDY POPULATION

The research was carried out in three centers specialized in the treatment of people living with HIV/AIDS located in the northwestern of the state of São Paulo. At the Care Center for Infectious and Parasitic Diseases (CADIP) in the county of Fernandópolis, and at the Specialized Assistance Service (SAE) of the counties of Jales and Santa Fé do Sul. Individuals with a diagnosis of HIV infection aged 50 or older were investigated. The following were excluded from the study: 1) people living with HIV under the age of 50; 2) those who did not have ART withdrawal between the months of September and December 2019; 3) those who did not accept to participate in the survey after reading the Informed Consent Form (ICF) (annex1); 4) those who started ART less than a year ago; 5) those who did not carry out viral load tests in the last six months before the application of the questionnaire; and 6) those who used only antiretroviral drugs or who used other drugs less than a year after the questionnaire was applied.

This study was approved by the Research Ethics Committee with opinion number 3.519.831.

Fig. 1 – Flowchart of people living with HIV/AIDS over the age of 50 included in the study



2.2 STUDY'S DESIGN

In this cross-sectional study, a structured questionnaire administered by professionals responsible for dispensing antiretroviral drugs after reading and accepting the ICF was applied, data from the results of laboratory tests were also consulted, as well

as the patients' ART was confirmed in medical records. The questionnaire contained epidemiological data, issues involving adherence to ART, names of antiretroviral therapy medications, names of other medications in continuous use for over a year, value of tests for HIV viral load (using the Real Time PCR/Abbott method), CD4 T lymphocyte count, antiretroviral treatment time, and comorbidities.

After data collection, drug names were entered into the University of Liverpool's drug interactions website (https://www.hiv-druginteractions.org/)[18]. This website provides a report on drug interactions and classifies the clinical significance of each according to a color system: red ("these drugs should not be co-administered"), amber ("potentially clinically significant interaction that may require additional monitoring, change in drug dosage or time of administration"), yellow ("weak potential for interaction with unlikely need for additional monitoring or dose adjustment"), and green ("no clinically significant interaction"). Medicines that did not exist on the website list were excluded. All patients with drug interactions were analyzed for viral load. Virological failure was defined in individuals with the last two HIV viral load tests above 200 copies/ml.

2.3 DATA ANALYSIS

The data obtained were stored in a Microsoft Excel spreadsheet and a descriptive analysis of the data was performed.

3 RESULTS

According to the data provided by the surveyed services, there is a prevalence of 37.19% of people over the age of 50 in the HIV/AIDS segment.

Among the 113 included in the survey, 65.49% were in the age group of 50 to 59 years old, 20.35% between 60 and 69 years old, 12.39% between 70 and 79 years old, and 1.77% over 80 years old. The mean age was 58.75 (standard deviation 7.2).

Regarding age at diagnosis of HIV, 43.36% acquired the disease after 50 years of age and 56,74% before.

As for the time of these people living with the virus, 32.74% have lived with the virus for 5 years, 23% for 6 to 10 years, 35.40% for 11 to 20 years, and 8.85% between 21 and 30 years.

Regarding sex and education, 51.33% were female and 48.67% male, 3.5% had no level of education, 51.33% had incomplete elementary school, 16.82% had complete

elementary school, 3.54% had incomplete high school, 13.27% had complete high school, 9.73% had complete higher education, 0.88% had incomplete higher education, one case was ignored due to the lack of response in the questionnaire.

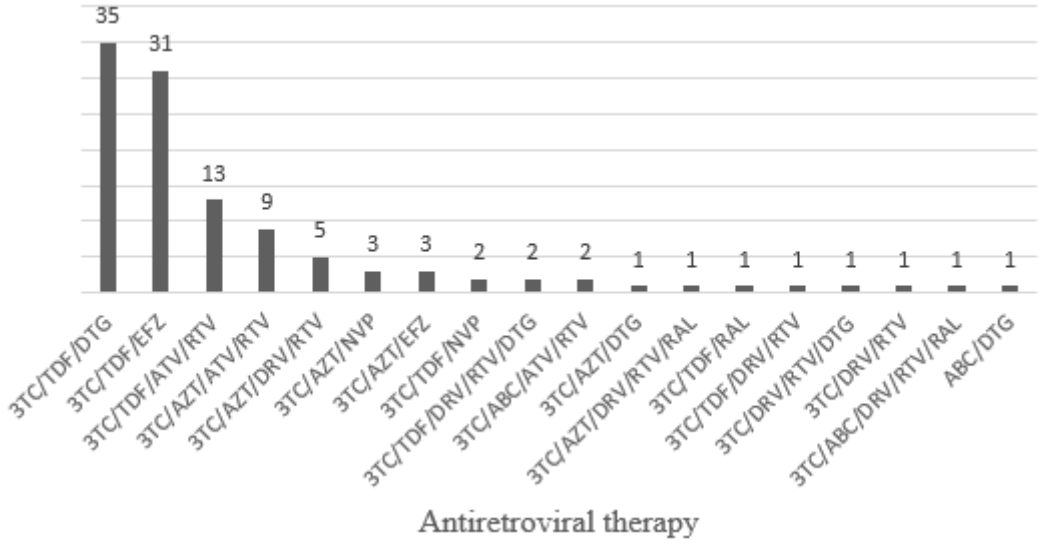
Regarding comorbidities, only 10.62% had no comorbidities, 40.71% had one, 31.86% two, 10.62% three, 6.18% four or more. The most common comorbidities are described in table 1.

Tabela 1. Main comorbidities reported in the questionnaires

Comorbidities	Percentage
Systemic Arterial Hypertension	47,79%
Diabetes Mellitus	20,35%
Depression	17,70%
Dyslipidemia	13,27%
Hypothyroidism	9,73%
Heart disease	7,08%
Anxiety disorder	5,53%
Bipolar disorder	4,42%
Prostatic hyperplasia	3,54%
Panic syndrome	3,54%
Epilepsy	2,65%
Gastritis	2,65%
Peripheral Vascular Insufficiency	2,65%

Among the ART regimens used, only two case made use of a dual regimen, the others made use of schemes with three or more antiretrovirals and the most used associations were with nucleoside analog reverse transcriptase inhibitors (NRTI) associated with an inhibitor from Integrase (INI) or with non-nucleoside analog transcriptase inhibitors (NNRTIs) or with Protease Inhibitors (PI).

Fig. 2 - ART scheme for the 113 individuals included in the study: Lamivudine (3TC); Tenofovir (TDF); Dolutegravir (DTG); Efavirenz (EFZ); Atazanavir (ATV); Ritonavir (RTV); Zidovudine (AZT); Darunavir (DRV); Nevirapine (NVP); Abacavir (ABC); Raltegravir (RAL).



Among the 113 included in the study, 25.66% used a medication in addition to ART, 23.89% used two, 18.58% used three, 14.6% used four, 17.70% used 5 or more medications.

In our study, there were 74.34% of individuals with drug interactions, with 7.08% having red interactions. There was a total of 124 drug interactions, 50 of these were yellow interactions, 66 were amber, and 8 were red (Table 2).

Drugs involving the central nervous system were responsible for most of the interactions (47.58%) followed by antihypertensive drugs (25.8%), hypoglycemic agents (7.25%), and statins (5.64%). Among antiretrovirals, the classes of protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) showed the highest number of drug interactions.

Regarding adherence to their antiretroviral therapy, 5.3% reported not taking their medication most days, 32.74% said they have already stopped taking their medication and 61.95% answered that they never stopped taking ART.

The results of tests for HIV viral load and LT CD4 count revealed that most individuals had LT CD4 above 500 cells/mm3 and undetected HIV viral load (less than 40 copies/ml).

Table 3 - Values of CD4 T lymphocytes and HIV viral load

LT CD4 value - cells/mm ^{3}	**n ° - % of individuals**	
Above 500	75 - 66.38%	
Between 350 - 500	22 - 19.47%	
Between 200 - 349	12 - 10.62%	
Between 100 - 199	3 - 2.65%	
Less than 100	1 - 0.88%	
HIV viral load value-copies/ml	**n ° - % of individuals**	**n ° - % of individuals**
	Last CV	**Penultimate CV**
Not detected < 40	101 - 89.38%	101 - 89.38%
40 – 1000	9 - 7.96%	9 - 7.96%
1001 – 10,000	1 - 0.88%	2 - 1.77%
Above 10,000	2 - 1.77%	1 - 0.88%

The table 4 reveals the main drug interactions found in our research according to the University of Liverpool's drug interactions website[18].

Table 4. Most common amber drug inteactions and red drug interactions

Interaction	**Antiretroviral**	**Other drugs**	**Interaction description**	**n°**
Red	Atazanavir/ Ritonavir	Quetiapine	It may increase concentrations of Quetiapine. Risk of prolongation of the QT interval on the electrocardiogram.	3
	Atazanavir/ Ritonavir	Omeprazole	May reduce concentration and effectiveness of ATV/RTV	1
	Atazanavir/ Ritonavir	Budesonide	May increase corticosteroid concentrations, switch to beclomethasone suggested	1
	Darunavir/ Ritonavir	Domperidone	May increase Domperidone concentrations and side effects such as increased QT interval	1
	Nevirapine	Phenobarbital	May reduce NVP levels and cause loss of therapeutic effect with possible development of resistance	1
Amber	Efavirenz	Clonazepam	May reduce Clonazepam concentrations	9
	Dolutegravir	Metformin	Increases Metformin concentrations	6
	Atazanavir/ Ritonavir	Clonazepam	May increase Clonazepam concentrations	5
	Efavirenz	Atorvastatin	May reduce Atorvastatin concentrations	4

	Efavirenz	Levothyroxine	May increase Levothyroxine elimination, monitor TSH	4
	Darunavir/ Ritonavir	Clonazepam	May increase Clonazepam concentrations	3
	Dolutegravir	Atenolol	May increase Atenolol concentrations	3
	Atazanavir/ Ritonavir	Amitriptyline	May increase Amitriptyline concentrations, risk of prolongation of the QT interval	2
	Atazanavir/ Ritonavir	Diazepam	May increase the effects of Diazepam	2
	Atazanavir/ Ritonavir	Lithium	May reduce lithium concentrations, risk of prolonging the QT interval	2
	Darunavir/ Ritonavir	Atorvastatin	May increase Atorvastatin concentrations and may cause myopathy	2
	Atazanavir/ Ritonavir	Propranolol	May increase the concentrations of Propranolol	2

Of the 113 included in the study, 110 (97.34%) had no virological failure, 3 (2.65%) had virological failure (the last two viral load tests above 200 copies/ml) and drug interactions. Table 5 shows the cases defined as virological failure.

Table 5 - Cases of virological failure

Case	ART	Comedications	Last Viral Load copies/ml	Penultimate viral load copies/ml	As for adherence, have you ever stopped taking your medication?
1	3TC/TDF ATV/RTV	Losartan	10680	8158	Approximately more than half the time
2	3TC/TDF ATV/RTV	Amitriptyline	53317	513	Approximately more than half the time
3	3TC/TDF EFZ	Amitriptyline Diazepam	229	877	Not once

4 DISCUSSION

According to the present study, in these three centers specialized in the care of PLHIV, 37% of individuals in the segment with the disease are in the age group of 50 years or more. In the United States (USA), in 2009, this age group represented 33% and it was estimated that by 2020 it would be more than half of the cases[19].

Among those included in the study, there is a predominance of women with little difference between genders. In Brazil, the number of infected men is greater than the

number of women, but national data show that in this age group there is a lower ratio between genders, being 1.8 men for each woman[4]. This study revealed that the low level of education coincides with the profile found in individuals with AIDS in Brazil[4].

Regarding adherence to ART, taking medication with a frequency of at least 80% is considered sufficient adherence to achieve viral suppression and maintenance[15]. In this study, 38% of those surveyed reported failure in adherence, this data is very variable among national studies and may present a rate of 18% to 74.3%[20]. There is a difference between the methods of assessing adherence, in the same study the rate of non-adherence varied from 22.9%, 31.9%, and 74.3% according to medical records, self-report, and pharmaceutical records, respectively[21].

The most widely used ART schemes were composed of two nucleoside reverse transcriptase inhibitors combined with an integrase inhibitor or a non-nucleoside reverse transcriptase inhibitor or a protease inhibitor, these being the most widely used schemes in the world and following the Brazilian protocol [15,22].

Polypharmacy is common in people over 50 [23,24]. In a Brazilian study, 26.5% of the elderly used drugs with potential drug interaction [25]. However, when the sample is made up of people living with HIV, this potential increases due to ART reaching 68% [17].

As we have found in our research, others that have already been carried out also show that comorbidities such as cardiovascular diseases, especially hypertension, dyslipidemia, and diabetes become highly prevalent among HIV-infected patients [19,26,27,28]. Furthermore, we also corroborate with other studies regarding the high prevalence of diseases such as depression, anxiety disorder, and other mental illnesses [17,19].

Pharmacokinetic interactions between ART and other concomitant drugs are common and can lead to an increase or decrease in exposure to drugs, reducing the effectiveness of ART or increasing its toxicity[15]. In this study, we noted that most drug interactions occur with classes of antiretroviral drugs such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors (Table 2). These classes are inhibitors and inducers of the cytochrome P450 (CYP) enzyme system [19]. The introduction of Ritonavir to increase the bioavailability of most protease inhibitors, increased the risk of clinically significant drug interactions, Ritonavir is an extremely potent inhibitor of CYP 3A4 and 2D6, which metabolize almost 70% of all drugs that are metabolized by the CYP450. Protease and non-nucleoside reverse transcriptase inhibitors may also affect the activity of glycoprotein P, a transport protein that prevents the accumulation of toxins [19].

The services researched in this study are within the global goal of the Joint United Nations Programme on AIDS, which has set global targets so that 90% of people on antiretroviral treatment should have their viral loads suppressed in 2020. However, in the United States, 20% of people living with HIV who have been linked to cares or are on ART remain virologically without suppression [29].

In this study, we defined virological failure as the inability to maintain suppression of viral replication at a level below 200 copies/mL [22]. Sporadic detection of low viremia (less than 200 copies/mL) represents, in most cases, replication of wild viruses from infected latent cells[15]. An isolated measure of HIV Viral Load detectable among undetectable measures, defined as a viral blip, does not constitute a virological failure [30]. However, persistent low viremias can be the result of an emergence of resistance and predicted failure of ART. Persistent viremia with more than 200 copies/mL generally represents virological failure [31].

There were only three cases defined as virological failure (Table 5). In case 1, there was an interaction classified as amber between Atazanavir/Ritonavir and Amitriptyline in an individual with failed ART adherence. This interaction has the potential to increase the concentrations of tricyclic antidepressants [15,18,22]. Amitriptyline is metabolized predominantly by CYP2D6 and CYP2C19 and ATV/RTV can potentially increase exposure to Amitriptyline and cause side effects [18]. When administering both drugs, monitoring of the electrocardiogram is indicated due to the risk of prolongation of the QT interval [18]. In addition, it may be necessary to change the dose of Amitriptyline and monitor the effects of the drug based on clinical evaluation and drug concentration [22].

The second case also fails to adhere to ART and the drug interaction is considered yellow between Atazanavir/Ritonavir and Losartan [18]. Losartan is bioactivated mainly by CYP2C9 [18,32]. This drug is metabolized by CYP3A4 inhibitors such as protease inhibitors and should be used with caution in combination [32]. Ritonavir is a modest inducer of CYP2C9 and ATV/RTV can increase the conversion to the most pharmacologically active metabolite[18]. A prior dose adjustment is not recommended [18].

In the last case (case 3), the patient reports good adherence to ART and the interaction is classified as amber between Efavirenz and Diazepam. Diazepam is a benzodiazepine class drug, this class is widely used worldwide, in a study carried out in the metropolitan region of São Paulo it was observed a prevalence of use of

benzodiazepines of 3.6% in the general population and 7.8% among subjects with a mental health condition [33].

Diazepam is metabolized to nordiazepam by CYP3A4 and 2C19 and additionally by temazepam, mainly by CYP3A4. Efavirenz can potentially decrease exposure to Diazepam. In these cases, there is a need to monitor the clinical effect and withdrawal symptoms [18]. All non-nucleoside reverse transcriptase inhibitors are metabolized in the liver by the CYP3A isoenzymes. Co-administration with drugs that induce or inhibit these enzymes can alter the concentrations of NNRTIs, resulting in virological failure or adverse effects [34]. Therefore, this interaction needs to be better studied, as it could interfere with antiretroviral treatment and be the cause of virological failure. The HIV genotyping test should be ordered in cases of treatment failure. In the latter case, the individual has the last viral load with 229 copies/ml, and it is not possible to perform the exam, since the genotyping tests available for use in Brazil have been validated for viral load values above 500 copies/mL [15].

For all suspected cases of virological failure, it is initially suggested to correct adherence failures, repeat a viral load test, evaluate the pharmacological interactions that lead to a decrease in the concentration of antiretroviral drugs, and in the need to change the antiretroviral regimen, consult a resistance specialist [15].

In the current global home confinement situation due to the Coronavirus COVID-19 outbreak, most individuals are exposed to an unprecedented stressful situation of unknown duration. This may not only increase daytime stress, anxiety and depression levels, but also disrupt sleep [35]. The increase in the number of psychotropic drugs during the pandemic should also be monitored in HIV patients due to the increased risk of drug interactions.

As in this research, in a Swiss cohort study we observed a large number of drug interactions in people living with HIV, in addition, we also noticed that there was no adverse effect on the effectiveness of ART and most interactions affected co-medications [17].

The evaluation of the interaction with dose adjustment showed benefits in reducing viral load in another study [36] .

Online tools can help doctors reduce the risks of these drug interactions. More than a third of clinically significant drug interactions may not be correctly identified by physicians [16]. For this reason, online tools should be easily available in all PLHIV care settings.

Although the measures used can only identify potential drug interactions, it does not mean that all potential interactions or inappropriate drugs will result in adverse results, they do identify concerns that should be monitored [28].

Further studies should be carried out to improve the scientific evidence between these interactions and their interference in the treatment of HIV and other diseases.

5 CONCLUSION

In our study, we noted that drug interactions are very prevalent among individuals with HIV/AIDS over 50 years of age and that these interactions have the potential to mainly alter the concentration of comedications and have no significant impact on virological failure.

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