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RESEARCH ARTICLE

Monitoring plasmatic concentrations of efavirenz for prediction of clinical outcomes in people living with HIV

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Abstract

Objective: To assess the ability of efavirenz plasma concentrations to predict clinical outcomes. **Methods:** This is a cross-sectional study in people living with HIV on efavirenz antiretroviral therapy. The ROC curve (*Receiver Operating Characteristic*) analysis was carried out in order to verify the variation in sensitivity and specificity between the efavirenz plasma concentration and the other variables of interest in the study. The study was approved by the Human Research Ethics Committee of the University of São João del-Rei, Central-West Dona Lindu Campus, as per CAAE 41775015.3.0000.5545. **Results**: Among the 108 patients included in the study, the median age was 54.5 years (IQ25%: 41.0; IQ75%: 63.0). The efavirenz plasma concentration was not able to predict outcomes such as viral suppression (AUC: 0.525; CI95%: 0.334 - 0.716; p = 0.803), immune response (AUC: 0.501; CI95%: 0.390 - 0.612; p = 0.982), presence of adverse events (1 adverse event - AUC: 0.326: CI95%: 0.156 - 0.497; p = 0.103) / ≥ 4 adverse events – AUC = 0.432; CI95%: 0.323 - 0.542; p = 0.232) and adherence (AUC = 0.537; CI95%: 0.423 - 0.651; p = 0.520). **Conclusions:** More studies are needed to estimate the relationship between clinical outcomes and efavirenz plasma concentrations in current clinical protocols. Therefore, the accumulation of evidence on the subject is essential to identify the feasibility of therapeutic monitoring of antiretrovirals for the purpose of optimizing parameters such as efficacy, safety and adherence.

Keywords: Drug Monitoring; Efavirenz; Viral Load; CD4 Lymphocyte Count; Drug-Related Side Effects and Adverse Reactions.

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INTRODUCTION

Currently, 25.4 million people have access to antiretroviral therapy worldwide[1]. In Brazil, full and free access to antiretrovirals was instituted in the 1990s and recent estimates indicate that about 630 thousand people are undergoing treatment. This distribution system for antiretroviral therapy in the country is a prominent model on the world stage, especially for the universality of access[2,3].

The current clinical protocol indicates the combination of three antiretrovirals, two Nucleoside Analog Reverse Transcriptase Inhibitors (NARTI) associated with another class, such as a Non-Nucleoside Analog Reverse Transcriptase Inhibitor (NNARTI), a Protease Inhibitor with Ritonavir booster (PI/r), or an Integrase Inhibitor (INI). Efavirenz, an antiretroviral belonging to the NNARTI class, has been included in the preferred treatment regimen for many years, however current recommendations for initial therapy suggest replacing efavirenz with dolutegravir. Despite this update in the clinical protocol, efavirenz is still an antiretroviral widely used in the country, as it remains the first choice for patients co-infected with tuberculosis, pregnant women or those with the possibility of becoming pregnant, and patients with intolerance or contraindication to dolutegravir[4].

The therapeutic range of efavirenz associated with effectiveness ranges from 1 to 4 µg/mL. Consequently, subtherapeutic concentrations become responsible for the failure in viral suppression and impaired effectiveness, while supratherapeutic concentrations result in increased toxicity and potentiate adverse events, and may even cause treatment interruption[5-7]. Therapeutic drug monitoring (TDM) is a process capable of defining the dosage regimen necessary to maintain plasma concentrations within the therapeutic range[8]. In Brazil, TDM is not a routine tool in the treatment of people living with the Human Immunodeficiency Virus (HIV). In this regard, it is known that one of the criteria necessary to assess the viability of TDM in clinical practice is the existence of a definable relationship between plasma concentration and the expected clinical outcome for a given drug[9,10].

In the current scenario, there is a lack of consensus on the impact of TDM in the treatment of HIV infection. The literature covers numerous studies that highlight the relevance of TDM to enhance antiretroviral therapy in terms of effectiveness and safety[11-14], however, other studies point to the need for more robust evidence that can justify TDM in routine clinical management in people living with HIV[15-18]. In this context, investigating the relationship between plasma concentration and clinical outcomes is essential to determine whether therapeutic monitoring of antiretrovirals can be useful in clinical practice. Therefore, the present study aims to assess the ability of efavirenz plasma concentrations to predict clinical outcomes.

METHODS

Study design

This is a cross-sectional study, conducted in patients on antiretroviral therapy with regimens containing efavirenz were evaluated in relation to plasma concentrations achievement. The structuring of this study was based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[19].

Sampling

This is a sub study of a larger research project that aimed to evaluate efavirenz pharmacokinetics in adults and older adults with HIV/AIDS. For the development of the study, the sample size calculation was based on the inter-individual variability of efavirenz plasma concentrations found in an analysis involving adults and elderly people on antiretroviral therapy[20]. A coefficient of variation of 54.8% for both groups and a difference up to 4 mg/L was considered for the calculation, since the therapeutic range of efavirenz varies between

1.0 and 4.0 mg/L[20]. After the inclusion of the data previously described in the OpenEpi® program, it was observed that the ideal sample should contain a total of 108 patients.

Study location

The study was conducted with patients seen at the Specialized Assistance Service (*Serviço de Assistência Especializada* - SAE) in the city of Divinópolis in the Brazilian state of Minas Gerais. This institution is a reference for the 55 municipalities in the Center-West macro-region of Minas Gerais and provides comprehensive care to users through a multidisciplinary team that involves nurses, pharmacists, doctors, psychologists, social workers, among others.

Study participants

Patients aged 18 years or older using the following therapeutic regimens were included: Scheme 1 ("zidovudine; lamivudine; efavirenz", with one 300 mg tablet of zidovudine + lamivudine 150 mg, administered twice a day and one 600 mg tablet of efavirenz, administered once daily); Scheme 2 ("tenofovir, lamivudine; efavirenz", one 300 mg tablet of tenofovir + lamivudine 300 mg + efavirenz 600 mg, administered once daily). Patients were recruited between September 2016 and August 2017, being approached in the waiting room for care of the SAE and invited to participate in the study. Upon accepting participation and meeting the inclusion criteria, patients being conducted for data collection through interviews and review of medical records, and subsequently forwarded for the collection of blood samples. Pregnant and lactating patients and patients with renal and hepatic insufficiency were defined as exclusion criteria, due to the presence of physiological and clinical alterations in these populations. All hospitalized and prison patients were defined as ineligible due to the difficulty of access to them.

Blood sample collection, processing, and analysis

Blood sample collections were carried out in two stages, with a minimum interval of one hour between the first and the second collection in order to estimate the plasma trough concentration (C_{min}). All blood samples (4mL) were collected through the brachial vein, in EDTA tubes, approximately 24 ± 2 hours after administration of the last dose of efavirenz. These collections were performed in an appropriate room for handling biological material, by a pharmacist participating in the research. The pharmacist responsible for the collections was trained and followed the routine of blood sample collection by the professionals of the institution during the period of one month, before the beginning of the study. After collection, the samples were kept under refrigeration until the last collection of the day and then sent to the Analytical Laboratory of the Federal University of São João del-Rei, Central-West Dona Lindu Campus, for the separation of plasma into refrigerated centrifuge at 4°C (2000 rpm; 20 minutes) and storage at -80°C until the moment of analysis. Subsequently, efavirenz was quantified in order to check the presence of the drug in concentrations below, above, or within the therapeutic range (1 to 4 µg/mL). Efavirenz was quantified using high performance liquid chromatography with visible ultraviolet detection (HPLC-UV), using an analytical method previously developed and validated. The analyzes were performed considering the mobile phase acetonitrile: water (pH 3.2) (68: 32, v/v), flow rate of 1.0 mL min-1, injection volume of 20 µL and Phenomenex® Gemini C18 column (250 mm × 4.6 mm, 5 µm), C18 Agilent ZORBAX Reliance Cartridge pre-column, and 260 nm wavelength[21]. The investigator responsible for efavirenz quantification remained blind to all clinical outcomes under analysis during the study period, in order to minimize potential biases.

Variables of interest in the study

Sociodemographic characteristics

To characterize the sociodemographic profile of the study population, the following variables were collected: age, gender, skin color or tone, literacy, level of education, fixed income.

Efavirenz plasma concentration

The efavirenz plasma trough concentration was predicted using the equation defined by Winter (2010)[22]: $C_{mín} = e^{-[Kel (Tmín - T1) - ln C1]}$.

In this equation, Kel represents the elimination constant calculated two hours after drug administration; $T_{mín}$ is the time required for the minimum concentration, according to the frequency of dose administered (12, if 12 in 12 hours or 24, if once a day); T_1 refers to the time of the first collection in relation to the administered dose; ln C_1 consists of the natural logarithm of the plasma concentration of the first collection.

When estimating plasma concentrations for patients in which the values of concentration 1 (C_1) or concentration 2 (C_2) were lower than the limit of quantification (LQ) and for patients in whom a single blood sample was collected, the mean of the Kel values of the other individuals was considered. In cases where C_1 and C_2 were smaller than the LQ, Kel and C_{min} were defined as not detectable. In the cases where C_{min} resulted in values below 0.001 from the application of the formula, this parameter was considered to be equal to 0.

Viral load

Viral load was categorized as "detectable (≥ 40 copies/mL) and undetectable (<40 copies/mL)", according to the detection limit defined by the laboratory responsible for the analyzes. Viral load values < 40 copies/mL were defined as viral suppression. For each patient, the last test result issued was selected up to six months before the recruitment date.

CD4+ T lymphocyte count

The CD4+ T lymphocyte count was categorized as "< 500 cells/μL and ≥ 500 cells/μL", since the 500 cell/μL count is the threshold for the definition of different stages of HIV infection[23]. In this case, the last test result issued up to six months before the recruitment date was considered.

Adverse events to antiretroviral therapy

Adverse events to antiretroviral therapy were measured from all incidents or undesirable occurrences associated with the use of antiretrovirals that resulted in damage to patients[24,25], which were identified through self-reporting in interviews, information in medical records, and changes in laboratory exams. This variable was categorized into the number of adverse events (at least one adverse event/four or more adverse events to antiretroviral therapy), since this refers to the cutoff point defined by national studies aimed at analyzing adverse events in people living with HIV[26,27].

Adherence to current antiretroviral therapy

Data on adherence to antiretroviral therapy were obtained from interviews with patients, through the application of a form based on questions developed by the Antiretroviral Treatment Adherence Project, a national project structured to direct the collection of specific data about the people living with HIV in the Brazil[27]. At the time of the interviews, the patients were asked: "Thinking about the last month, did you stop taking any dose of any of the antiretroviral drugs in use in any part of the day?". From the adherence checklist, patients

answered the following options: “never”, “only once”, “sometimes”, “often”, “very often”, “always”. For the performance of statistical analyzes, this variable was categorized as “non-adherent” and “adherent”. Patients who answered the options “sometimes”, “often”, “very often” or “always” were considered non-adherent, while patients who answered the options “never” or “only once” were considered as adherent.

Data Analysis

Initially a descriptive analysis of the study population was performed, in which patients had their sociodemographic, pharmacotherapeutic, and clinical characteristics represented by means of median, interquartile range (IQ), and frequency distribution. The Kolmogorov-Smirnov test was used in order to verify the normality of the data for the numerical variables. The variable plasma efavirenz concentration was categorized into two groups: concentrations in the therapeutic range ($C_{mín}$ 1 to 4 µg/mL) and concentrations outside the therapeutic range ($C_{mín}$ < 1 µg/mL and > 4 µg/mL). Both groups were compared for pharmacotherapeutic and clinical variables using the chi-square test. The ROC curve (Receiver Operating Characteristic) analysis was performed in order to verify the variation in sensitivity and specificity between the efavirenz plasma concentration and clinical outcomes of interest in the study (viral suppression; immune response; presence of adverse events to antiretroviral therapy; adherence to antiretroviral therapy). In view of the analysis of binary variables, the following prediction rule was considered: cut-off point Y=1, in which the values above are classified as the presence of the outcome and the values below are classified as the absence of the outcome. Therefore, for the purpose of classifying and measuring the number of positive and negative predictions, a value of 1 was assigned for the presence of outcomes and a value of 0 for the absence of outcomes. The area under the curve (AUC) values were evaluated for each of the clinical outcomes under analysis. The data obtained were stored in Microsoft Excel® files (2016) and exported to the Statistical Package for the Social Sciences® (SPSS) software (version 19.0). It is noteworthy that the missing data were disregarded for the execution of the statistical analyses.

Ethics statement

The study was approved by the Human Research Ethics Committee of the Federal University of São João del-Rei, Central-West Dona Lindu Campus, as per CAAE 41775015.3.0000.5545. All patients included in the study were invited to sign the free and informed consent term.

RESULTS

The study population consisted of 108 patients, all on antiretroviral therapy regimens containing efavirenz. Patients aged between 22 and 82 years were included, being observed median age of 54.5 years (IQ25%: 41.0; IQ75%: 63.0). There was a predominance of male patients (51.9%) and who declared themselves brown (50.0%). The other sociodemographic data are shown in Table 1.

Table 1. Sociodemographic data of patients on antiretroviral therapy with regimes containing efavirenz - Divinópolis, Brazil (2016-2017) (n = 108)

VARIABLES	N	%
Age (years)	54.5 (41.0 ; 63.0)[a]	
Gender		
Female	52	48.1
Male	56	51.9
Skin color or tone		
White	34	31.5
Black	17	15.7
Brown	54	50.0
Other	3	2.8
Literacy		
No	15	13.9
Yes	93	86.1
Level of education		
< 8 years	66	61.1
≥ 8 years	42	38.9
Fixed income		
No	14	13.0
Yes	94	87.0

[a]Values represented by median and interquartile range (IQ25%; IQ75%).

Most patients (53.7%) were on antiretroviral therapy with the triple dose combined regimen in a single tablet (tenofovir + lamivudine + efavirenz). Concerning adverse events to antiretroviral therapy identified through self-reports in interviews, information in medical records and changes in laboratory tests, it is noteworthy that 92.6% of patients had at least one adverse event. It was also observed that 41.7% had a number equal to or greater than four adverse events related to antiretrovirals in use. A total of 340 adverse events were identified, among which nightmares (15.0%) and vertigo (13.5%) were the most frequent. With regard adherence to antiretroviral therapy, it was possible to verify that 63.9% of the interviewed patients declared themselves to be adherent (Table 2).

Additionally, according to the investigation of clinical data, 91.7% of patients had an undetectable viral load (< 40 copies/mL) and 63.9% had the T CD4+ lymphocyte count ≥ 500 cells/μL. However, analysis of the efavirenz plasma concentration showed that 88.0% of the patients had subtherapeutic levels (Table 2). The median efavirenz plasma concentration was 0.0146 μg/mL (IQ25%: 0.0011; IQ75%: 0.1318), with minimum and maximum quantification values ranging from 0 to 16.31 μg/mL.

Table 2. Distribution of pharmacotherapeutic and clinical characteristics of patients on antiretroviral therapy with regimes containing efavirenz - Divinópolis, Brazil (2016-2017) (n=108)

VARIABLES	TOTAL		Plasma concentration in the therapeutic range		Plasma concentration outside the therapeutic range		p-value
	N	%	N	%	N	%	
Antiretroviral therapy in use							
AZT + 3TC / EFV	50	46.3	7	77.8	43	43.4	0.048*
TDF + 3TC + EFV	58	53.7	2	22.2	56	56.6	
Presence of at least one adverse event to antiretroviral therapy							
No	8	7.4	1	11.1	7	7.1	0.658
Yes	100	92.6	8	88.9	92	92.9	
Presence of four or more adverse events to antiretroviral therapy							
No	63	58.3	7	77.8	56	56.6	0.217
Yes	45	41.7	2	22.2	43	43.4	
Adherence to antiretroviral therapy							
Non-adherent	39	36.1	4	44.4	35	35.4	0.587
Adherent	69	63.9	5	55.6	64	64.6	
Carga viral atual							
Detectável	9	8.3	1	11.1	8	8.1	0.753
Indetectável	99	91.7	8	88.9	91	91.9	
Linfócito T CD4+ atual							
< 500 células/μL	39	36.1	3	33.3	36	36.4	0.856
≥ 500 células/μL	69	63.9	6	66.7	63	63.6	

* $p < 0,05$. Statistical: Chi-square. Abbreviations: AZT - Zidovudine. EFV - Efavirenz. TDF - Tenofovir. 3TC - Lamivudine.

The AUC obtained for all parameters evaluated was less than 0.6, demonstrating the inability of the efavirenz plasma concentration to predict the clinical outcomes in the study population. For viral load (Figure 1a) and CD4+ T lymphocyte count (Figure 1b) the AUC values were 0.525 (CI95%: 0.334 - 0.716, p = 0.803) and 0.501 (CI95%: 0.390 - 0.612, p = 0.982), respectively. The analysis of adverse events showed the worst AUC values. For the presence of at least one adverse event to antiretroviral therapy (Figure 1c) an AUC of 0.326 (CI95%: 0.156 - 0.497, p = 0.103) was observed and for the presence of four or more adverse events to antiretroviral therapy (Figure 1d) an AUC of 0.432 (CI95%: 0.323 - 0.542, p = 0.232). Regarding adherence to antiretroviral therapy an AUC of 0.537 (CI95%: 0.423 - 0.651, p = 0.520) was obtained.

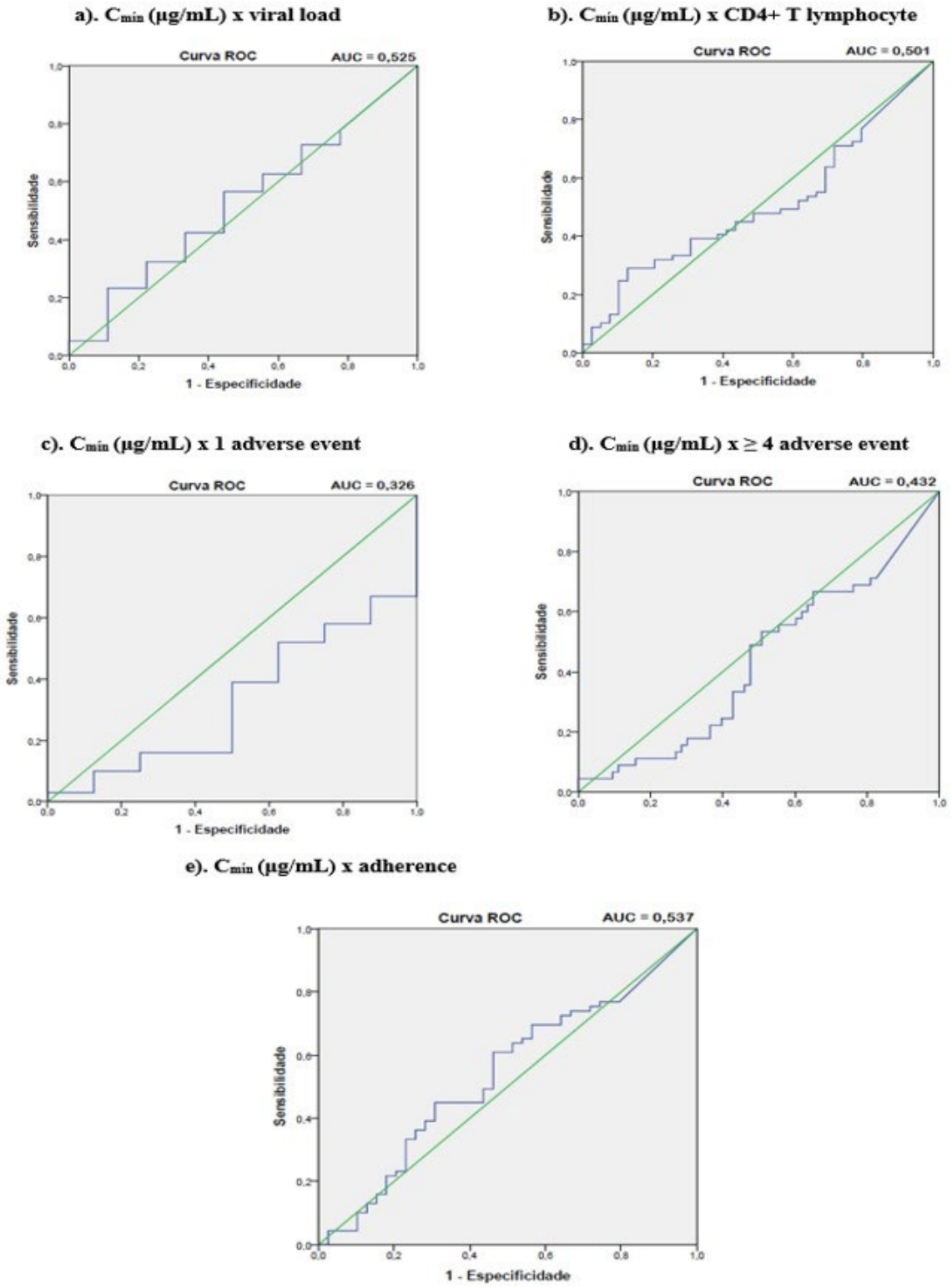

Figure 1. Analysis of the ROC curve between efavirenz plasma concentration and variables of interest in the study: a). viral load; b). CD4+ T lymphocytes count; c). presence of an adverse event to antiretroviral therapy; d). presence of four or more adverse events to antiretroviral therapy; and e). adherence to antiretroviral therapy

The results described demonstrate that the sensitivity and specificity obtained, as well as the AUC values observed, did not result in the prediction of the clinical outcomes under analysis.

DISCUSSION

Currently, limited information regarding the relationship between the plasma concentration of antiretrovirals and clinical outcomes in people living with HIV is available nationally and internationally. To the best of our knowledge this is the first study to assess the prediction of clinical outcomes by monitoring plasma concentrations of efavirenz in the Brazilian population. In this regard, it is important to consider that Brazil has one of the most modern policies for tackling Acquired Immunodeficiency Syndrome (AIDS), as provides universal access to antiretroviral therapy via the Public Health System (*Sistema Único de Saúde* - SUS)[28,29]. Therefore, in a country that invests widely in free access to antiretrovirals and in clinical support for patients, it is highlighted that the development of studies capable of investigating the relationship between plasma concentrations and clinical outcomes is essential to elucidate the usefulness of TDM, and thus, support clinical decision making, providing means to minimize the use of resources and improve public health management.

In the present study, the efavirenz plasma concentration was unable to predict outcomes such as viral suppression (AUC: 0.525; CI95%: 0.334 - 0.716; p = 0.803), immune response (AUC: 0.501; CI95%: 0.390 - 0.612; p = 0.982), presence of adverse events (1 adverse event - AUC: 0.326: CI95%: 0.156 - 0.497; p = 0.103) / ≥ 4 adverse events - AUC = 0.432; CI95%: 0.323 - 0.542; p = 0.232), and adherence (AUC = 0.537; CI95%: 0.423 - 0.651; p = 0.520), limiting the recommendation for therapeutic monitoring in the population under analysis. There are studies that corroborate our findings, indicating the inability to predict clinical outcomes through efavirenz plasma concentrations[30-32]. However, there is evidence that demonstrates an important concentration-response relationship for efavirenz, supporting the relevance of TDM in the routine of patients on antiretroviral therapy with regimens containing this drug. Gutiérrez et al.[33], when evaluating efavirenz plasma concentrations, found AUC values corresponding to a satisfactory prediction of outcomes such as effectiveness and toxicity (AUC > 0.6). Marzolini et al.[5] demonstrated that plasma concentration is an important predictor of clinical outcomes in patients undergoing efavirenz therapy, since plasma levels less than 1 µg/mL and greater than 4 µg/mL were associated with therapeutic failure and the presence of adverse events, respectively. In the study conducted by Gounden et al.[34] and Mukonzo et al.[35], it was also possible to identify the existence of a relationship between efavirenz plasma concentrations and toxicity, in which patients with higher plasma levels developed a greater number of adverse events associated with the central nervous system. Orrell et al.[36], observed that efavirenz plasma concentrations are predictive of outcomes such as failure of viral suppression, which suggests the ability of TDM to potentialize the effectiveness of this antiretroviral.

Some limitations of the present study may have an influence on the low capacity of efavirenz plasma concentrations to predict clinical outcomes under analysis. Among them, the use of self-reporting stands out as one of the devices to measure outcomes such as adverse events and adherence. Self-reporting is an adequate source for obtaining information about the patient, but it is considered as a non-objective method that may be subject to conditions of attention, memory and convenience[37,38]. In addition, the determination of adverse events and adherence through self-reporting in scenarios with a predominance of a low level of education, as observed in the study population, may result in the loss of sensitivity of the method in question. Generally, people with less education have greater difficulty in attributing undesirable effects as a result of the use of drugs, causing greater difficulty in understanding when asked about treatment[39,40]. In this respect, an alternative capable of assisting in obtaining information regarding antiretroviral therapy in patients with a low level of education is the association of self-reporting with other complementary resources[41]. Another limiting characteristic of this study is the fact that patients were assessed for adverse

events and adherence considering antiretroviral therapy as a whole, and these parameters were not investigated specifically for efavirenz. In view of these perspectives, Marzinke[42] and Cattaneo et al.[14] demonstrate TDM as an ideal resource for monitoring adverse events and adherence, since the insertion of this method in clinical practice is capable of directing strategies to individually identify and prevent both toxicity and discontinuation of treatment with antiretrovirals.

It is worth noting that for the prediction of outcomes in patients on antiretroviral therapy in environments with scarcity of resources, there are clinical monitoring strategies considerably effectiveness. Outcomes such as viral suppression, reconstitution of the immune response and adherence can be predicted by periodic assessment of viral load and CD4+ T lymphocyte counts[43]. Pharmacy dispensing data and pill counts in clinical care are also good predictors of adherence in this scenario[44]. In addition, laboratory evaluation of metabolic, hepatic and renal changes is an important means of identifying adverse events resulting from antiretroviral treatment[45].

With regard to the therapeutic range defined for efavirenz (1 to 4 µg/mL), it was observed that 88.0% of the study patients had subtherapeutic concentrations (<1 µg/mL). In this case, an important aspect to be considered is the presence of adverse conditions in the pre-analytical phase capable of compromising the drug quantification process[46]. In order to avoid interference in the analysis, a flow was defined to standardize the steps of collection, transport, processing and storage of samples, after the training period of the researcher involved in the pre-analytical phase of the study. Appropriate techniques for collecting blood samples were considered to avoid the presence of alterations such as hemolysis, for example. There was a plan to carry out the collections at specific times, in order to estimate the plasma concentration of efavirenz in the valley. To avoid exposing the samples to conditions with the potential to cause drug instability, the samples were kept refrigerated (4 °C) until the time of plasma separation in a centrifuge and stored at 80 °C until the time of analysis. In addition, we disregarded the inactivation of the virus by heating the sample to 60 °C, as is usually done in antiretroviral quantification studies, a condition capable of compromising the stability of efavirenz[47]. Therefore, the strategy considered in our study to avoid contamination was wearing personal protective equipment (PPE) and other alternative biosecurity measures. During the analytical phase, we also performed the stability analysis of efavirenz to ensure the reliability of the results regarding the plasma concentrations achieved[21].

Still dealing with the identification of subtherapeutic concentrations in most patients under study, it is worth noting the high intra- and inter-individual variability observed in analyzes of patients on efavirenz therapy[20,48,49]. It is well established in the literature that conditions such as age, ethnicity, weight and genetic polymorphism are highly responsible for changes in the pharmacokinetics of efavirenz[50-56]. In addition, food and drug interactions also act as determining factors for changes in efavirenz pharmacokinetic parameters. According to Bernardes et al. (2021)[57], antiretrovirals with a highly lipophilic character, such as efavirenz, have a greater absorption potential when administered in association with food. Lopez-Cortés et al.[58] demonstrates a considerable reduction in plasma concentrations of efavirenz in the presence of drugs such as rifampicin, commonly used together due to the high incidence of co-infection between the tuberculosis virus and HIV.

Despite the high number of patients undergoing sub-therapy, the vast majority reported adherence to treatment and had an undetectable viral load. This result reflects the benefits of synergism between the combined antiretrovirals, since viral suppression can be obtained even in situations where the concentration of one of the drugs is below the therapeutic range. However, it is worth noting that the repeated exposure of patients on antiretroviral therapy to subtherapeutic levels is worrying, since it can result in the development of resistance. In this context, the importance of dose adjustment guided by TDM is reaffirmed for the maintenance of plasma concentrations of antiretrovirals within the therapeutic range[5,59]. In addition, it is known that antiretroviral options for treatment are limited, and it is essential to manage them with caution to avoid viral resistance. In this case, the application of TDM has a

high potential to ensure that patients receive optimal doses of antiretrovirals from the beginning of therapy, preventing resistance and prolonging the effectiveness of existing treatment options[60].

After a thorough analysis of the literature, few studies were found to predict variables related to HIV infection using the assessment of sensitivity and specificity through the ROC curve[32,33], however the investment in this type of analysis is of fundamental importance to generate inferences regarding the theme.

CONCLUSIONS

The determination of efavirenz plasma concentration did not show sufficient sensitivity and specificity to predict clinical outcomes such as viral suppression, immune response, presence of adverse events and adherence in the study population. The study has limitations and, therefore, the findings are not sufficient to support the application of TDM in the routine of patients on antiretroviral therapy with regimes containing efavirenz. New studies are needed to estimate the relationship between clinical outcomes with efavirenz plasma concentrations and other antiretrovirals recommended in current clinical protocols. Therefore, the accumulation of evidence on the subject is essential to identify the feasibility of therapeutic monitoring of antiretrovirals for the purpose of optimizing parameters such as efficacy, safety and adherence.

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Authors' contributions

CS and TLSS conceived and planned the study. TLSS carried out the data collect presented in the manuscript; CS and TLSS performed the statistical analysis and interpreted the data; CS and TLSS wrote the paper; CS, TLSS, NSS, GMR, KBB, CAMP, ES reviewed and edited successive versions; TLSS, CS, NSS, GMR, KBB, CAMP, ES approved the final version.