Atazanavir/ritonavir vs Efavirenz as the first line of treatment in adults living with HIV

Atazanavir/ritonavir vs Efavirenz como primeira linha de tratamento em adultos vivendo com HIV

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ABSTRACT: *Introduction:* New antiretroviral therapy (ART) regimens for HIV could improve clinical outcomes for patients and to change the natural history of the infection. National and international guidelines currently recommend starting the treatment of infected individuals to prevent the deterioration of the immune system and to control viral replication, and prevention of the transmission of HIV infection. *Objectives:* to analyze the use of antiretroviral therapy those who include Atazanavir/ritonavir (ATV/r) or Efavirenz (EFV) in the first line of treatment for adult patients living with HIV. *Material and Methods*: a retrospective cohort study between August 2019 to July 2020 and focused on the Clinical Immunology Service/day Hospital of the *Instituto de Medicina Integral Prof. Fernando Figueira – IMIP*. The data were taken from the records selected at random and recorded in standardized questionnaires with subsequent transcription in computerized spreadsheets. The project was approved by the Human Research Ethics Committee (CEP) of IMIP/PE. The data were transcribed in the Excel program, analyzed on Epi Info™. Results: 131 patients participated in the study using EFV or ATV/r as the third drug in the antiretroviral regimen, 73.3% of whom were EFV patients and 26.7% using ATV/r. Initial viral suppression was observed in 88% (p > 0.05) of patients, regardless of the regimen used. Schemes containing ATV/r showed a prevalence of 47.1% of adverse effects and EFV 52.1% (p < 0.001). Conclusion: The findings of this study suggest that both ATV/r and EFZ showed similar effectiveness when used as a first line of treatment.

Keywords: Antiretroviral Therapy Highly Active; Effectiveness; Safety; Efavirenz; Atazanavir; HIV.

RESUMO: *Introdução:* Novos regimes de terapia antirretroviral (TARV) para HIV podem melhorar os resultados clínicos para os pacientes e de alterar a história natural da infecção. Os guidelines nacionais e internacionais recomendam atualmente a iniciar o tratamento dos indivíduos infectados para prevenir a deterioração do sistema imunológico e controlar a replicação viral, e consequente prevenção da transmissão da infecção pelo HIV. *Objetivo*: Analisar o uso da terapia antirretroviral que incluem Atazanavir/ritonavir (ATV/r) ou Efavirenz (EFV) na primeira linha de tratamento de pacientes adultos vivendo com HIV. *Material e Métodos*: O presente trabalho consiste em um estudo coorte retrospectivo. A coleta de dados ocorreu no período de agosto de 2019 a julho de 2020 e se concentrou no Serviço de Imunologia Clínica/Hospital-Dia do Instituto de Medicina Integral Prof. Fernando Figueira - IMIP. Os dados foram retirados dos prontuários selecionados de maneira aleatória e registrados em questionários padronizados com posterior transcrição em planilhas computadorizadas. O projeto foi aprovado pelo Comitê de Ética em Pesquisa em Seres Humanos (CEP) do IMIP/PE. Os dados foram transcritos no programa Excel, analisados no Epi Info™. *Resultados*: 131 pacientes participaram do estudo utilizando EFV ou ATV/r como terceira droga do esquema antirretroviral, sendo 73,3% pacientes EFV e 26,7% usando ATV/r. A supressão viral inicial foi observada em 88% (p > 0,05) dos pacientes, independentemente do esquema utilizado. Esquemas contendo ATV/r apresentaram uma prevalência de 47,1% de efeitos adversos e EFV 52,1% (p < 0,001). *Conclusão*: Os achados do desse estudo sugerem que tanto ATV/r quanto o EFV apresentaram efetividade semelhante quando utilizados como primeira linha de tratamento.

Palavras-chave: Terapia antirretroviral de alta atividade; Efetividade; Segurança; Efavirenz; Atazanavir; HIV.

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INTRODUCTION

Since the advent of antiretroviral therapy (ART), several studies have demonstrated over time the benefit of starting treatment earlier and earlier, altering the natural history of the infection, preventing the deterioration of the immune system and controlling replication, and consequent prevention of transmission of HIV infection[1]. Actually, the main treatment guides in the world, including the Brazilian, indicate ART at the time of HIV infection diagnosis, regardless of CD4+ T cell count, viral load and presence of symptoms[2]. However, barriers to access to ART patients living with HIV (PLHIV) exist with important differences between countries, especially according to socioeconomic levels and models of organization of health systems[3-7].

For naive patients on antiretroviral treatment, the Brazilian guide[8-10], actually recommends starting ART schemes using two Nucleotide analog reverse-transcriptase inhibitors (NRTIs), with the Ministry of Health and World Health Organization (WHO) recommending Lamivudine (3TC) and Tenofovir (TDF), associated with an Integrase Inhibitor (INIs), Dolutegravir (DTG)[9,10].

Antiretroviral regimen composed of two NRTIs and a protease inhibitor (PI) - atazanavir - boosted with ritonavir (ATV/r) demonstrated excellent efficacy in controlling viral replication, good durability in treatment naive patients and a high genetic barrier to resistance and it has relatively few metabolic adverse effects[9]. ATV/r has better gastrointestinal tolerance and less impact on glycolipid metabolism, in addition to being the only PI not associated with increased cardiovascular risk. It also presents the best dosage, as the use of a single daily dose, enables better treatment adherence[11,12].

The main adverse effects of ATV/r are reversible indirect hyperbilirubinemia, with or without jaundice, but without the concomitant hepatic elevations of transaminases, nephrolithiasis, nephrotoxicity and cholelithiasis[12-16]. It is worth noting that ATV requires acidic gastric pH for dissolution[17].

Efavirenz (EFV), a non-analogous nucleoside reverse transcriptase inhibitor (NRTI), may be a great choice for some patients, although this drug has a low genetic barrier, facilitating the development of resistance[9]. EFV has a long history of widespread use globally, and its minimal interaction with rifampicin has become an option for patients who need concomitant treatment for tuberculosis (TB)[9]. It is worth noting that EFV can cause central nervous system (CNS) side effects such as abnormal dreams, dizziness, pain headache and depression, which resolve over a period of days to weeks in most patients; elevation of LDL cholesterol and triglycerides, in addition to a prolongation of the QT interval[18,19].

Studies evaluating the effectiveness and safety of different antiretroviral regimens for the treatment of HIV infection can support the recommendations of current national and international protocols that are based on studies of effectiveness. Thus, the aim of the study was to analyze the use of antiretroviral therapy that include Atazanavir/ritonavir or Efavirenz in the first line of treatment for adult patients living with HIV.

MATERIALS AND METHODS

This is a retrospective cohort study of HIV-1 patients using ART. The study covered data collected from medical records of patients seen at the Clinical Immunology Service/Day-*Hospital at Institute of Integral Medicine Professor Fernando Figueira* (IMIP), Brazil.

Were eligible subjects diagnosed with HIV infection, of both sexes and aged above 18 years in the use of antiretroviral regimens containing ATV/r or EFV as first line treatment. In addition to these medications, depending on the individual regimen, everyone included in the study used Lamivudine and Tenofovir. These should be monitored by the Specialized Assistance Service/Day-Hospital (SAE/DH) between April 1996 and October 2018, with 25 people who used Atazanavir/ritonavir and 61 who used Efavirenz started treatment before 2014. In addition, all participants in this study had at least one result of a plasma viral load test for HIV-1 RNA (CV RNA HIV-1) and LT CD4 + and six months of follow-up.

Were excluded, PLHIV who had started ART in other services, previous prophylactic use of ARVs, patients with coinfections with hepatitis B and C, HTLV, pregnant women, people with leprosy and defining neoplasms still under treatment, in addition to chronic and cardiac renal failure and liver, autoimmune diseases, dyslipidemia and use of corticosteroids, before the start of ART.

The patients' medical records were obtained through random non-probabilistic sampling, on the premises of the SAE/DH medical file and, using the Microsoft Excel 2017 program, random numbers were generated, establishing the order of verification.

Data were collected between March 2019 and December 2019, using information from clinical records, the computerized system of laboratory test reports and the System Laboratory Tests Control of the National Network of Lymphocyte Count CD4+/CD8+ and viral Load (SISCEL). Through SISCEL, it was possible to verify LT CD4+ and CV RNA HIV-1 counting exams until 2011 and results of genotyping and ARV dispensing per patient from 2011.

Patients were followed for the entire period they used ARVs of interest for the study, the end of use being considered through the exchange report in the medical record with the dates confirmed by the information from SISCEL. The data were recorded

in a computerized spreadsheet, based on a previously standardized questionnaire containing sociodemographic information (date of birth, city of residence, ethnicity, sex, marital status, sexual orientation, education, occupation and income); behavioral and lifestyle habits (smoking, drinking, use of illicit drugs and being a sex worker); clinical and laboratory data (transmission, opportunistic infections, presence of chronic diseases prior to ART and initial clinical classification, according to the adapted Centers for Disease Control and Prevention [CDC] criteria)[20,21] results of laboratory tests and genotyping); HAART used (time between diagnosis and start of HAART, time on HAART use, therapeutic regimen, adherence reported by the doctor in the medical record and confirmed by SICLOM records, adverse effects and therapeutic failures) and co-infections (hepatitis B and C, syphilis , HTLV, toxoplasmosis, cytomegalovirus and tuberculosis).

Therapeutic effectiveness was defined as maximum viral suppression six months after the start of treatment. The maximum limit of detection in viral load assays used during the study period varied between ≤ 400 copies/ml (up to 2004), ≤ 50 copies/ml (up to 2013) and ≤ 40 copies/ml (to the present day)[19]. Immune recovery (increased CD4+ LT levels) during follow-up was also assessed. The safety parameter for the use of ART included reporting in medical records of adverse effect, motivating or not the exchange of antiretroviral drugs.

This research was approved by the Human Research Ethics Committee of Institute of Integral Medicine *Professor Fernando Figueira* - IMIP (CAAE 00172318.9.000.5201).

All analyzes were performed using the Epi Info version 7.0 for Windows statistical package. Descriptive statistics were used to present the data using mean and 95% confidence interval (CI) (normal distribution) or median and interquartile range (IIQ, non-normal data) for numerical variables and relative frequency distribution for categorical variables. To compare antiretrovirals, Pearson's chi-square test was used for categorical variables and for continuous variables, the Kruskal-Wallis test (non-normal data) followed by Dunn's post-hoc test, the significance p value used was $p < 0.05$.

RESULTS

In the beginning, 396 adult HIV-1 patients who were being followed up at SAE/DH were eligible to participate in the study. However, 265 patients were excluded, according to the study's eligibility criteria. In the end, 131 patients participated in the study using EFV or ATV/r as the third drug in the antiretroviral regimen, with 96 (73.3%) patients using EFV and 35 (26.7%) patients using ATV/r.

The demographic and social characteristics of the participants included in the survey are shown in Table 1. Considering the total number of participants, the median

age was 39 years (IIQ = 33-44); 86.26% lived in the capital or metropolitan region of Recife (RMR), while 13.74% were from other cities in the state of Pernambuco; 54.96% were female, for whom the transmission of HIV-1 occurred through heterosexual sex, while in men the exposure category for HIV-1 infection in men who have sex with men (MSM), corresponded to 38,98% of men ($p < 0.05$).

Table 1. Sociodemographic data. Recife-PE, Brazil, 2020

	n	%
Gender		
Male	59	45.04
Female	72	54.96
Sexual orientation		
Heterosexual	103	81.75
Bi/homosexual	23	18.25
Ethnicity		
White	22	18.03
Not white	100	81.97
Marital status		
Married/stable union	68	66.02
Not married/widower/divorced	35	33.98
Scholarity		
≤ 8 years	52	46.43
> 8 years	60	53.57
Occupation		
Employee/Student	49	40.83%
Unemployed/retired /Away (INSS)	71	59.17%
Smoking		
Yes	12	10.26
No	105	89.74
Alcoholism		
Yes	8	6.84%
No	109	93.16%
Use of illicit drugs		
Yes	2	1.53%
No	129	98.47%
Sex worker		
Yes	3	2.29%
No	128	97.71%
Income		
Up to 1 minimum wage	45	54.22%
More than 1 minimum wage	38	45.78%

Subtitle: *INSS - Instituto Nacional do Seguro Social* (Brazil).
Source: Study data.

As for the comorbidities reported before the start of ART, it can be observed that there was no difference between the groups (p > 0.05), with psychiatric disorder being registered in 4.58% (n=6) of the patients, 6.84% (n=8) alcoholism, 3.82% (n=5) with systemic arterial hypertension, 1.53% (n=2) with reports of illicit drug use, 0.76% (n=1) diabetes type 2 melitus and 0.76% (n=1) some neoplastic disorder.

Before the start of treatment with the studied drugs, of AIDS-defining diseases, according to the CDC[20], it was possible to identify in the Efavirenz group a neurotoxoplasmosis with a presentation of 7.2% and among users of Atazanavir esophageal candidiasis with 5,9%. However, when the Rio de Janeiro Caracas criterion was observed[21], the most reported symptom was anemia and/or lymphopenia, affecting 55.1% of patients.

When observing the average number of days between the diagnosis of HIV and the beginning of ART, a great difference was observed for the beginning of the antiretroviral regimen after its indication. Individuals who used EFV started treatment earlier, with an average of 119 (IIQ = 30-705) days, with a difference of 121 days in relation to those who used ATV r (p > 0.275), who started treatment only after an average of 240 (IIQ = 83-1191) days from the date of diagnosis (Table 2).

However, no difference can be identified in the time of use of both Efavirenz and Atazanavir/ritonavir, since in both situations the use was observed for 204 weeks, with IIQ = 98-293 for ATV/r and IIQ 118-363 for EFV.

As for the laboratory characteristics of patients before starting ART (Table 2), the ATV/r group had a higher CD4+ LT count compared to the initial EFV count (p = 0.038). However, it is noteworthy that 59.3% of patients had CD4+ LT levels below 350 cells/mm³ in both groups.

There were also no differences in the values of CV RNA HIV-1 at the beginning of treatment for the ARVs involved in this study (p = 0,06), either in the number of copies of HIV RNA or in the base 10 logarithm (log 10).

There was a reduction in CV RNA HIV-1 and an increase in LT CD4+, when comparing the pre-treatment period and the last examination recorded in the medical record (p < 0.05). There was no significant difference in CV RNA HIV-1 of patients using ATV/r when compared to the median values achieved by patients using EFV (p < 0.05) in the last exam.

Initial viral suppression was observed in 88% of patients, regardless of the scheme used, with no difference between groups (p > 0.05). The median time between the start of ART and the first test showing viral suppression was 184 days for the ATV/r group and 147 days for EFV.

Table 2. Characteristics related to antiretroviral therapy, clinical and laboratory of patients before the start of treatment and in the last laboratory examination performed using antiretroviral. Recife-PE, Brazil, 2020

Variables	Total	ATV/r (n=35)	EFV (n=96)	p[a]
Time between diagnosis and initiation of antiretroviral therapy (days), median and (IIQ)	179.5	240 (83-1191)	119 (30-705)	0.275
Antiretroviral use time (days), median	1467	1505	1429	0.548
T CD4+ lymphocytes (cells/mm³), median				0.,038
Pre-treatment	335	380	291	
Last exam	657	701	614	
T CD4+ lymphocytes (%), median				0.291
Pre-treatment	18	19	17	
Last exam	30	30	31	
Plasma viral load of HIV-1 RNA				
Pre-treatment (copies/ml), median	30090	15760	44421	0.06
Last exam, (n), % de undetectable	209 (79.1)	674	4302	0.870
Viral suppression (%)				
Yes	110 (88)	28 (84.4)	82 (88.2)	
No	15 (12)	4 (12.5)	11 (11.8)	
Time to deletion (days)**,** median	155	184	147	0.103

Subtitle: ATV/r, atazanavir enhanced with ritonavir; EVF, Efavirenz;
[a]Teste Kruskal Wallis H seguido do post-hoc de Dunn
Source: Study data.

Considering the combination of viral suppression and absence of adverse effects, ATV/r was superior (p < 0.001), with 50.0% of patients without such events, while EFV, in which there was therapeutic effectiveness and no effect adverse in 42.7% of patients. Schemes containing ATV/r showed a prevalence of 47.1% of adverse effects and EFV 52.1%. It appears that the most prevalent adverse reactions for the scheme containing ATV/r were jaundice (17.6%), nausea and dyslipidemia (both with n=4; 11.5%), while for EFV, dizziness (13.5%) and insomnia (12.5%) were the most frequently reported (Table 3).

Table 3. Prevalence of adverse effects. Recife-PE, Brazil, 2020

Adverse effects	ATV/r (n=34) n (%)	EFV (n=96) n (%)
Diarrhea	2 (5.9)	2 (2.1)
Headache	1 (2.9)	8 (8.3)
Dizziness	1 (2.9)	13 (13.5)
Depression	-	8 (8.3)
Nightmares	-	6 (6.3)
Elevation of triglycerides	-	3 (3.1)
Skin rash	1 (2.9)	5 (5.2)
Insomnia	-	12 (12.5)
Anemia	2 (5.9)	-
Emotional lability	1 (2.9)	12 (12.5)
Asthenia	-	2 (2.1)
Suicidal thinking	-	2 (2.1)
Nausea	4 (11.8)	6 (6.3)
Lipodystrophy	1 (2.9)	5 (5.2)
Jaundice	6 (17.6)	-
Glucose intolerance	1 (2.9)	1 (1.0)
Dyslipidemia	4 (11.8)	7 (7.3)
Vomiting	2 (5.9)	3 (3.1)

Subtitle: ATV/r, atazanavir enhanced with ritonavir; EVF, Efavirenz;
Source: Study data.

DISCUSSION

The results of this study show that most people seen at the Day-Hospital/IMIP are women, on average, 39 years old, which differs from the data published in the latest epidemiological bulletin released by the Ministry of Health[22]. In this, it is observed the Brazilian population living with HIV is made up mostly of men aged between 20 and 34 years. The epidemiological bulletin of the Government of the State of Pernambuco found that heterosexual transmission was responsible for HIV infection among women in the state[23]. However, among men, the most common route of transmission was homosexual. Data which corroborate with the present study.

In a randomized, multicentre controlled clinical trial with 103 patients, there was a 63% viral suppression of ATV/r in triple therapy, which demonstrated in the long term that the effectiveness of monotherapy with ATV/r was lower when compared to triple therapy containing ATV/r[24]. This finding differed from the result of the present study, in which viral suppression occurred regardless of the ART used, with viral suppression observed in 184 days for the ATV/r group. As well as, the clinical trial showed a divergent result, with regard to the occurrence of adverse effects, considering the occurrence in 8% of patients in the monotherapy arm and 4% in triple therapy (p = 0.436)[24]. However, in a retrospective cohort, a significant increase in total bilirubin was demonstrated among patients using ATV/r[25], being compatible with the results found in this study.

A phase IV clinical trial with 40 treatment naive patients showed a significant reduction in the viral load of the scheme containing EFV, and the effectiveness of ART would be 77.4%. In addition, there was a significant increase in the mean CD4+ LT count[26]. This trial showed a similar result with regard to viral suppression, taking into account the similarity of the results presented. In patients using EFV, dizziness (13.5%), insomnia (12.5%) and emotional lability (12.5%) were the most reported, equivalent data from the literature[26]. In systematic review and meta-analysis of network, which included 34.032 patients, showed that efavirenz was the best-connected treatment with the other Integrase Chain Transfer Inhibitors. In addition, in this meta-analysis, dolutegravir and raltegravir showed superior efficacy and tolerance to efavirenz regimens[27]. The importance of these data is due to the fact that the toxicity profile, as well as the occurrence of adverse effects of ART, may be related to the increase in the morbidity and mortality of PLHIV, as well as the increase in costs of health services[28].

Significantly, greater declines in HIV RNA and maximum control with these ARTs were evidenced, along with significantly greater increases in CD4+ T cells with up to 43 weeks of therapy. Despite a significantly greater increase in total bilirubin among patients using ATV/r, no other significant increase in adverse laboratory values between the two drugs. These data are compared to those found in a clinical trial that has been shown to be effective and safe in the treatment of HIV infection in treatment naive patients. However, there was a significant increase, but in normal ranges of total cholesterol, LDLc and glycemia; in addition, a significant increase in HDLc concentrations was observed. On the other hand, the concentrations of triglycerides, phosphates, calcium and waist measurements did not show significant changes[26].

This study has limitations related to the lack of complete records of information in the clinical record, minimized by checking the data with the available computerized systems. Furthermore, the difference between the numbers of individuals in each group, especially for the ATV/r group, may have hindered the comparative analysis between the other ARV.

CONCLUSION

It was possible to show that ATV / r and EFZ showed similar effectiveness when used as the first line of treatment. Adherence to treatment has been shown to be an independent protective factor for achieving viral suppression. In addition, the current study could benefit future patients who are indicated to start antiretroviral therapy as a treatment for HIV infection.

REFERENCES

1. Le T, Wright EJ, Smith DM, He W, Catano G, Okulicz JF, et al. Enhanced CD4+ T-cell recovery with earlier HIV-1 antiretroviral therapy. New Engl J Med. 2013;368(3):218-30. https://doi.org/10.1056/nejmoa1110187.

2. Word Health Organization (WHO). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2nd ed. Geneve; 2016. Available from: http://www.who.int/hiv/pub/guidelines/keypopulations-2016/en/

3. Hocqueloux L, Prazuck T, Avettand-Fenoel V, Lafeuillade A, Cardon B, Viard JP, et al. Long-term immunovirologic control following antiretroviral therapy interruption in patients treated at the time of primary HIV-1 infection. AIDS. 2010;24(10):1598-601. https://doi.org/10.1097/qad.0b013e32833b61ba

4. Saez-Cirion A, Bacchus C, Hocqueloux L, Avettand-Fenoel V, Girault I, Lecuroux C, et al. Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy. ANRS VISCONTI Study. PLoS Pathogens. 2013; 9(3):e1003211. https://doi.org/10.1371/journal.ppat.1003211

5. Tran BX, Fleming M, Do HP, Nguyen LH, Latkin CA. Quality of life improvement, social stigma and antiretroviral treatment adherence: implications for long-term HIV/AIDS care. AIDS Care. 2018;30(12):1524-31. https://doi.org/10.1080/09540121.2018.1510094

6. Jaiswal J, Singer SN, Lekas HM. Resilience and beliefs in the effectiveness of current antiretroviral therapies among recently disengaged low-income people of color living with HIV. Behav Med. 2019;46(1):75-85. https://doi.org/10.1080/08964289.2019.1570070.

7. Kalichman S, Mathews C, Banas E, Kalichman M. Alcohol-related intentional nonadherence to antiretroviral therapy among people living with HIV, Cape Town, South Africa.

AIDS Care. 2019;31(8):951-7. https://dx.doi.org/10.1080%2F09540121.2019.1587357.

8. UNAIDS Data 2018: Latin America - Country tables. Geneva: UNAIDS; 2019. Available from: https://www.unaids.org/sites/default/files/media_asset/unaids-data-2018_en.pdf.

9. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. EUA; 2019. Available from: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines.

10. Brasil. Ministério da Saúde. Secretaria de Vigilancia em Saude. Departamento de Vigilancia, Prevencao e Controle das Infecções Sexuais Transmissiveis do HIV/Aids e das Hepatites Virais. Protocolo Clínico e Diretrizes Terapêuticas para Manejo da Infecção pelo HIV em Adultos. Brasília: Ministério da Saúde; 2018. Disponível em: http://www.aids.gov.br/pt-br/pub/2013/protocolo-clinico-e-diretrizes-terapeuticas-para-manejo-da-infeccao-pelo-hiv-em-adultos.

11. Scott MH, Michael SS, Mauro S, Julio SGM, Robert TS, Donna MJ, et al. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society - USA panel. JAMA. 2006;296(7):827-43. https://doi.org/10.1001/jama.296.7.827.

12. Ford N, Calmy A, Mofenson L. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. AIDS. 2011;25(18):2301-4. https://doi.org/10.1097/qad.0b013e32834cdb71.

13. Ryom L, Mocroft A, Kirk O, Worm SW, Kamara DA, Reiss P, et al. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. J Infect Dis. 2013;207(9):1359-69. https://doi.org/10.1093/infdis/jit043.

14. Chan-Tack KM, Truffa MM, Struble KA, Birnkrant DB. Atazanavir-associated nephrolithiasis: cases from the US Foods and Drug Administration's Adverse Event Reporting System. AIDS. 2007;21(9):1215-8. https://doi.org/10.1097/qad.0b013e32813aee35.

15. Hamada Y, Nishijima T, Watanabe K, Komatsu H, Tsukada K, Teruya K, et al. High incidence of renal stones among HIV-infected patients on ritonavir-boosted atazanavir than in those receiving other protease inhibitor-containing antiretroviral therapy. Clin Infect Dis. 2012;55(9):1262-69. https://doi.org/10.1093/cid/cis621.

16. Rakotondravelo S, Poinsignon Y, Borsa-Lebas F, de la Blanchardière A, Michau C, Jantzem H, et al. Complicated atazanavir-associated cholelithiasis: a report of 14 cases. Clin Infect Dis. 2012;55(9):1270-2. https://doi.org/10.1093/cid/cis620.

17. Fauci AS, Longo DL, Hauser SL, Jameson JL, Loscalzo J. Harrison Medicina interna. 19a ed. Porto Alegre: Artmed; 2017. v.1.

18. Bristol-Myers Squibb. Sustiva package insert. 2016. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020972s049-021360s038lbl.pdf.

19. Abdelhady AM, Shugg T, Thong N, Lu JB, Kreutz Y, Jaynes HA, et al. Efavirenz inhibits the human ether-a-go-go related current (hERG) and induces QT interval prolongation in CYP2B6*6*6 allele carriers. J Cardiovasc Electrophysiol. 2016;27(10):1206-13. https://doi.org/10.1111/jce.13032.

20. World Health Organization (WHO). International statistical classification of health problems. 10th rev. Geneva; 2010. Disponível em: www.who.int/classifications/icd/en.

21. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância, Prevenção e Controle das Infecções Sexualmente Transmissíveis, do HIV/Aids e das Hepatites Virais. Critérios de definição de casos de AIDS em adultos e crianças. Brasília (DF): Ministério da Saúde; 2018. Disponível em: http://www.aids.gov.br/pt-br/node/57787.

22. Brasil. Ministério da Saúde. Boletim Epidemiológico HIV/Aids. Brasília: Secretaria de Vigilância em Saúde; 2020. Disponível em: http://www.aids.gov.br/pt-br/pub/2020/boletim-epidemiologico-hivaids-2020.

23. Pernambuco. Secretaria Estadual de Saúde. Secretaria de Vigilância em Saúde. Boletim Epidemiológico HIV/Aids de PE - situação epidemiológica da infecção pelo HIV em Pernambuco. Recife; 2017. Disponível em: http://portal.saude.pe.gov.br/sites/portal.saude.pe.gov.br/files/boletim_hiv_aids-pe_2017.pdf.

24. Galli L, Spagnuolo V, Bigoloni A, Monforte AD, Montella F, Antinori A, et al. Atazanavir/ritonavir monotherapy: 96 week efficacy, safety and bone mineral density from the MODAt randomized trial. J Antimicrob Chemother. 2016;71(6):1637-42. https://doi.org/10.1093/jac/dkw031.

25. Horberg M, Klein D, Hurley L, Silverberg M, Towner W, Antoniskis D, et al. Efficacy and safety of ritonavir-boosted and unboosted atazanavir among antiretroviral-naïve patients. HIV Clin Trials. 2008;9(6):367-74. https://doi.org/10.1310/hct0906-367.

26. Amariles P, Galindo J, Mueses-Marín HF, Castañeda C. Efectividad y seguridad del esquema genérico lamivudina/tenofovir y efavirenz en pacientes con VIH/SIDA naïve: estudio fase IV no aleatorizad. Cali-Colombia 2012-2014. Rev Chilena Infectol. 2019;36(1):32-40. http://dx.doi.org/10.4067/S0716-10182019000100032.

27. Kanters S, Vitoria M, Doherty M, Socias ME, Ford N, Forrest JI, et al. Comparative efficacy and safety of first-line antiretroviral therapy for the treatment of HIV infection: a systematic review and network meta-analysis. Lancet HIV. 2016;3(11):e510-e520. https://doi.org/10.1016/S2352-3018(16)30091-1.

28. Kindie E, Anteneh ZA, Worku E. Time to development of adverse drug reactions and associated factors among adult HIV positive patients on antiretroviral treatment in Bahir Dar City, Northwest Ethiopia. PloS ONE. 2017;14(8):e0221608. https://doi.org/10.1371/journal.pone.0189322.