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Incidence and factors associated with adverse drug reactions in a cohort of individuals starting dolutegravir or efavirenz

Incidência e fatores associados a reações adversas a medicamentos em uma coorte de indivíduos iniciando o uso de dolutegravir ou efavirenz

Incidencia y factores asociados con reacciones adversas a medicamentos en una cohorte de individuos que inician dolutegravir o efavirenz

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Jullye Campos Mendes
ORCID: https://orcid.org/0000-0003-3505-4626
Universidade Federal de Minas Gerais, Brazil
E-mail: jullyecampos@hotmail.com
Maria das Graças Braga
ORCID: https://orcid.org/0000-0002-4340-0659
Universidade Federal de Minas Gerais, Brazil
E-mail: mgbceccato@gmail.com
Adriano Max Moreira Reis
ORCID: https://orcid.org/0000-0002-0017-7338
Universidade Federal de Minas Gerais, Brazil
E-mail: amreis@outlook.com
Micheline Rosa Silveira
ORCID: https://orcid.org/0000-0001-7002-4428
Universidade Federal de Minas Gerais, Brazil
E-mail: michelinerosa@gmail.com

Abstract
Prospective cohort of people living with HIV who started combination antiretroviral therapy (cART) with regimens containing efavirenz (EFV) or dolutegravir (DTG) in three specialized HIV/AIDS care services in Belo Horizonte, Brazil, with the objective of analyzing incidence, time to development and factors associated with the first adverse drug reaction (ADR). Data were collected from September 2015 to October 2018 through face-to-face interviews, clinical records, and information systems. The ADR-associated factors were evaluated with Cox regression and the time to the first ADR with Kaplan-Meier survival curves. Among the 433 individuals included, 217 (50.1%) had ADR in 12 months of follow-up. Among the 695 registered ADRs, 604 (86.9%) occurred in individuals using the EFV-based regimen, and gastrointestinal, psychiatric, and nervous system disorders were the most frequent. The mean time to develop the first ADR was 210.6 days (95% CI: 195.5-225.8). The concomitant use of other medications was associated with a higher risk of ADR (HR: 2.00; 95% CI: 1.38-2.89). The use of alcohol (HR: 0.64; 95% CI: 0.49-0.85) and the DTG-based regimen (HR: 0.40; 95% CI: 0.28-0.58) were factors associated with a lower risk of ADRs. We conclude that the DTG-based regimen had a better safety profile than the EFV-based regimen at 12 months of follow-up. Clinical and behavioral characteristics were associated with higher ADR risks and should be monitored when managing the treatment of HIV.
Keywords: Drug-related side effects and adverse reactions; Antiretroviral therapy, highly active; HIV; Dolutegravir; Efavirenz.

Resumo
Coorte prospectiva de pessoas vivendo com HIV que iniciaram terapia antirretroviral (TARV) combinada com esquemas contendo efavirenz (EFV) ou dolutegravir (DTG) em três serviços de atenção especializada em HIV/AIDS de Belo Horizonte, Brasil, com o objetivo de analisar incidência, tempo até desenvolvimento e fatores associados à primeira reação adversa medicamentosa (RAM). Os dados foram coletados de setembro de 2015 a outubro de 2018 por meio de entrevistas face-a-face, prontuários e sistemas de informação. Os fatores associados à RAM foram avaliados com regressão de Cox e o tempo até a primeira RAM com curvas de sobrevida de Kaplan-Meier. Dentre os 433 indivíduos incluídos, 217 (50,1%) tiveram RAM em 12 meses de seguimento. Entre as 695 RAMs registradas, 604 (86,9%) ocorreram em indivíduos em uso do esquema contendo EFV, sendo as doenças gastrointestinais, psiquiátricas e do sistema nervoso as mais frequentes. O tempo médio para desenvolver a primeira RAM foi de 210,6 dias (IC 95%: 195,5-225,8). O uso concomitante de outros medicamentos foi associado à maior risco de RAM (HR: 2,00; IC 95%: 1,38-2,89). O uso de álcool (HR: 0,64; IC 95%: 0,49-0,85) e o regime contendo DTG (HR: 0,40; IC

95%: 0,28-0,58) foram fatores associados a um menor risco de RAM. Concluímos que o regime contendo DTG apresentou melhor perfil de segurança do que o regime contendo EFV aos 12 meses de seguimento. Características clínicas e comportamentais foram associadas a maiores riscos de RAM e devem ser monitoradas no manejo do tratamento do HIV.
Palavras-chave: Efeitos colaterais e reações adversas relacionados a medicamentos; Terapia antirretroviral de alta atividade; HIV; Dolutegravir; Efavirenz.

Resumen
Cohorte prospectiva de personas viviendo con VIH que iniciaron terapia antirretroviral (TARV) combinada con esquemas que contenían efavirenz (EFV) o dolutegravir (DTG) en tres servicios de atención especializada en VIH/SIDA en Belo Horizonte, Brasil, con el objetivo de analizar incidencia, tiempo de desarrollo y factores asociados a la primera reacción adversa a medicamentos (RAM). Los datos fueron recolectados de septiembre/2015 a octubre/2018 a través de entrevistas, registros clínicos y sistemas de información. Los factores asociados a RAM se evaluaron con regresión de Cox y el tiempo hasta la primera RAM con curvas de Kaplan-Meier. De los 433 individuos incluidos, 217 (50,1%) presentaron RAM en 12 meses de seguimiento. De las 695 RAM registradas, 604 (86,9%) ocurrieron en personas que usaban el régimen basado en EFV, y las más frecuentes fueron trastornos gastrointestinales, psiquiátricos y del sistema nervioso. El tiempo medio para desarrollar la primera RAM fue de 210,6 días (IC 95%: 195,5-225,8). El uso concomitante de otros medicamentos se asoció con mayor riesgo de RAM (HR: 2,00; IC 95%: 1,38-2,89). El consumo de alcohol (HR: 0,64; IC 95%: 0,49-0,85) y el régimen basado en DTG (HR: 0,40; IC 95%: 0,28-0,58) fueron factores asociados a un menor riesgo de RAM. Concluimos que el régimen basado en DTG tuvo un mejor perfil de seguridad que el régimen basado en EFV a los 12 meses de seguimiento. Las características clínicas y conductuales se asociaron con mayores riesgos de RAM y deben monitorearse al manejar el tratamiento del VIH.
Palabras clave: Efectos colaterales y reacciones adversas relacionados con medicamentos; Terapia antirretroviral altamente activa; VIH; Dolutegravir; Efavirenz.

1. Introduction

The combination Antiretroviral Therapy (cART) reestablishes the immune response, reducing opportunistic diseases and improving the quality of life of people living with HIV (PLWH) undergoing treatment (Antiretroviral Therapy Cohort Collaboration, 2008; HIV-Causal Collaboration et al., 2010; Pimentel et al., 2020). On the other hand, the need for continued use of cART triggers undesirable effects in individuals undergoing treatment. Adverse drug reactions (ADR) are frequently reported by individuals on cART and are associated with the therapeutic regimen and reduced adherence to treatment (Shet et al., 2014; Mendes et al., 2018; Cardoso et al., 2019; Carvalho et al., 2019).

In Brazil, the treatment of individuals diagnosed with HIV through the Brazilian National Health System is carried out per the recommendations of the Clinical Protocol and Therapeutic Guidelines (CPTG) of the Ministry of Health for the management of HIV infection, and the Brazilian government is responsible for dispensing the cART. The combination of efavirenz (EFV) plus tenofovir fumarate/lamivudine (TDF/3TC), in a fixed-dose, was recommended as the preferred regimen for starting cART from 2014 to 2017. As of 2017, these recommendations were updated, adopting as the first line of treatment the regimen containing dolutegravir (DTG) plus TDF/3TC (Batista et al., 2019), due to the high potency, the high genetic barrier for developing resistance, and the better safety profile of DTG compared to EFV (Patel et al., 2014; Molina et al., 2015; Walmsley et al., 2015).

EFV is a non-nucleoside reverse transcriptase inhibitor, and its use is associated with a high frequency of neuropsychiatric disorders, such as insomnia, headache, anxiety, and depression, followed by dyslipidemia, hepatic alterations, and skin lesions (Dai et al., 2020). DTG is a second-generation integrase strand transfer inhibitors, and its use is associated with a lower risk of ADR and gastrointestinal disorders such as diarrhea and nausea, followed by headache, insomnia, and liver disorders (Patel et al., 2014; Taha et al., 2015; Molina et al., 2015). While less frequent, neuropsychiatric disorders have also been reported using DTG (Kanters et al., 2020). In previous studies, factors associated with ADR in individuals using ARV regimens were advanced clinical classification of HIV infection (Kindie et al., 2017; Sherfa et al., 2021), Body Mass Index > 24 kg/m2 (Dai et al., 2020), being female, and using illicit drugs (Mendes et al., 2018).

Most of the data available on the safety of DTG were obtained from controlled, randomized clinical trials, highlighting the importance of conducting observational studies to assess drug safety in clinical practice. Thus, given the recent Brazilian updates on HIV treatment and the scarce data from real-life studies, it is necessary to longitudinally assess the safety of new antiretroviral (ARV) regimens used to start cART in Brazil. Thus, the objective is to evaluate the safety profile of these drugs in clinical practice and whether DTG has a better safety profile compared to EFV.

This study aims to analyze the incidence, the factors associated with the first ADR episode in individuals using ARV regimens containing EFV or DTG, in 12 months after the first dispensing, and time to the first ADR.

2. Methodology

Study design and locations

This prospective cohort study employed data from the ECOART project conducted in three public specialized care services for HIV/AIDS in Belo Horizonte in Minas Gerais State (Mendes et al., 2018; Cardoso et al., 2019; Pimentel et al., 2020). The services provide comprehensive treatment for PLWH and were identified as service I, II, and III, jointly responsible for about 80% of the dispensing of cART for PLWH in Belo Horizonte, the capital of a southeastern state from Brazil.

Service I is an outpatient service of a large hospital in the public health that provides hospital and outpatient care specializing in infectious diseases. Service II is a testing and counseling center and Specialized Assistance Service, linked to the Municipality of Belo Horizonte (MBH). Service III is a training and referral center for the care of infectious and parasitic diseases linked to the MBH.

The ECOART project was conducted as per Resolution N° 466/2012 of the National Health Council and approved by the Research Ethics Committee of the Federal University of Minas Gerais (CAAE 31192014.3.0000.5149) and of the services in which the study was conducted.

Study population and data collection

The study included individuals: (i) HIV-infected; (ii) aged 16 or over; (iii) cART treatment-naïve; (iv) who started using cART with up to six months of treatment; and (v) in follow-up at the evaluated health services and who attended the health service during the recruitment period for interviews of the ECOART project. We included individuals using the regimens efavirenz 600mg/tenofovir disoproxil fumarate 300mg/lamivudine 300mg (EFV/TDF/3TC) or dolutegravir 50mg/tenofovir disoproxil fumarate 300mg/lamivudine 300mg (DTG/TDF/3TC), main therapeutic regimens of the first line of treatment for HIV in people starting cART in Brazil during the period of data collection, and who had clinical records in health services.

Face-to-face interviews were conducted by a team of pharmacists and trained academics using a standardized questionnaire and forms. In the first interview, individuals were invited to participate in the study and signed an informed consent form. Baseline interview data from the ECOART project were used for this study.

Data were collected from September 2015 to October 2018, with the interviews were carried out in the first two years and the data from the medical records collected until the end of the follow-up. Sociodemographic and behavioral characteristics and the variable adherence to cART were collected from the interview. Clinical, laboratory, and pharmacological treatment-related characteristics were collected from the clinical records over 12 months from the start of cART. Information from laboratory tests and the antiretroviral regimen was complemented with the Laboratory Tests Control System of the National Network for the CD4+/CD8+ Lymphocyte Count and HIV Viral Load (SISCEL) and the Logistic Control System of Medicines (SICLOM), respectively.

Study variables

The dependent variable was ADRs registered in the clinical record, from the onset of cART to the 12 months of follow-up, and the time elapsed until the first ADR episode. The independent variables investigated were grouped as follows: (i) Sociodemographic characteristics: sex (female; male), age (in years), age group (16-19; 20-34; 35-49; 50-68), age dichotomized by the median (≤33 years old; >33 years old), self-reported skin color/ethnicity (brown; white; black; asian; indigenous), marital status (single/divorced/widowed; married/stable union), educational level (≤9; 10-12; 13 or more years of formal education), employed (yes; no), health insurance (yes; no), socioeconomic class (AB: high, C: intermediate, DE: low) and municipality of residence (Belo Horizonte; other); (ii) Behavioral characteristics and lifestyle habits: current alcohol use (yes; no), smoking (non-smoker; current smoker; former smoker), and use of any illicit drug in lifetime (yes; no); (iii) Clinical and laboratory characteristics: CD4 count at baseline (<200; 200-500; >500 cells/mm3) and viral load at baseline (≤100,000; >100,000 copies/mL), comorbidities (yes; no), AIDS-defining illness at baseline (A: asymptomatic; B: symptomatic; C: AIDS-defining conditions); Risk/exposure category (men who have sex with men; heterosexual men; heterosexual women; injecting drug use/others); (iv) Characteristics related to pharmacological treatment: antiretroviral regimen (EFV/TDF/3TC; DTG/TDF/3TC), treatment time until the event (in days), adherence to cART (yes; no), concomitant use of other non-ARV medications (yes; no) and ARV switch (yes; no).

The socioeconomic class was measured using the Brazilian Association of Research Companies (ABEP) criteria, which estimates the purchasing power of individuals according to the ownership of comfort items and the level of education of the head of the household. The economic class of individuals was categorized into high (A-B), intermediate (C), and low (D-E) (ABEP, 2008). Adherence to cART was measured through the adapted 8-item Morisky Medication Adherence Scale (MMAS-8), with written permission and approved license from the author. The MMAS-8 score ranging from 0 to 8. Individuals with 8 points were classified as adherent (de Oliveira-Filho et al., 2014).

The clinical classification of the stage of the disease when starting cART was evaluated using the adapted criteria of the Centers for Disease Control and Prevention (CDC), with individuals classified as asymptomatic (A), symptomatic (B), and AIDS-defining conditions (C) (CDC, 1992). Concerning multiple regression, the symptomatic and asymptomatic categories were unified to form the category without AIDS-defining conditions. The ARV switch variable was collected from SICLOM and defined as replacing some active ingredient initially prescribed in 12 months of follow-up. SICLOM is a computerized system that contains clinical data on people living with HIV undergoing treatment and all records of antiretroviral dispensation in the public health network in Brazil.

WHO's ADR definition was adopted (WHO, 1972). The ADRs reported in the clinical record were classified according to the Preferred Term (PT) and System Organ Class (SOC) levels of the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0, an international medical terminology developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (MSSO, 2021). Access to MedDRA was authorized at no cost as it was an academic study. Medications used concomitantly with ARVs were classified using the second level of the Anatomical Therapeutic Chemical (ATC) classification (WHO, 2020).

Data analysis

The population was descriptively analyzed, with frequency distribution for categorical variables and measures of central tendency and variability for quantitative variables. Data distribution normality was assessed using the Shapiro-Wilk test. The ADRs were analyzed per the ARV regimen, and the individuals were classified into two groups for the analyses: (i) EFV/TDF/3TC in fixed combined dose; and (ii) DTG/TDF/3TC. Subjects were evaluated according to the first prescribed treatment. ADR frequency was estimated at 12 months from the first cART dispensing.

The probability of surviving without ADR and mean time to the first ADR were estimated by the Kaplan-Meier survival curves. The Log-rank test was employed to assess the difference in survival distributions among individuals for categorical explanatory variables. ADR-associated factors were evaluated using multivariable Cox proportional hazards model, and hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated. Variables with a p-value ≤ 0.25 in the univariable analysis were included in the multivariable model. The backward stepwise method was employed to obtain the final model, keeping the variables with a p-value ≤ 0.05. Due to clinical relevance, the adherence variable was maintained in the multivariable model, even with a p-value > 0.05. Survival curves and Schoenfeld goodness-of-fit test were used for assessing the proportional hazards assumption. The goodness-of-fit of the final model was verified using the likelihood ratio and Wald and Score tests.

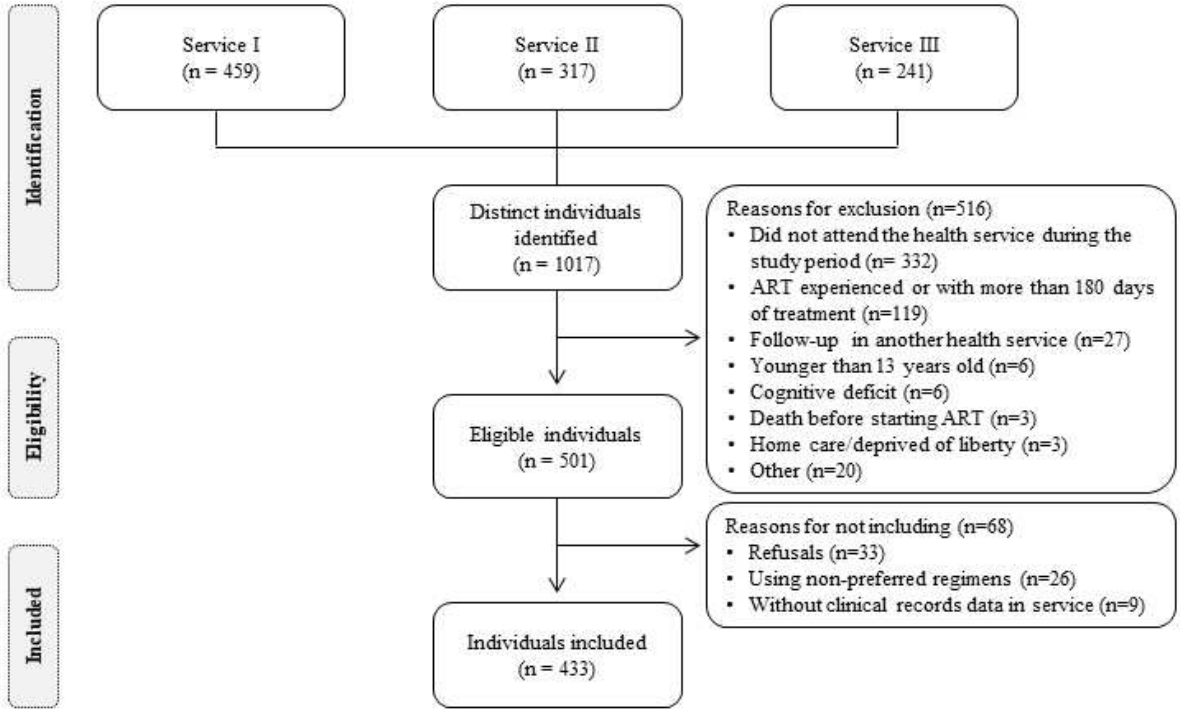
For the analysis of time until the first ADR, the individuals were followed up from the start date of cART and up to (i) the date of recording the ADR, (ii) the date of loss to follow-up, (iii) death, or (iv) end of 12-month follow-up. Thus, in the survival analyses, the first report of ADR to ARVs in the clinical record was considered an event of interest, and death and end of follow-up without the event were censored.

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 22.0 and R Project version 3.6.3, using the survival, survminder, ggplot2, and descr libraries. A significance level of 5% was considered in all analyses.

3. Results

A total of 433 individuals were included in the study, as shown in Figure 1.

Figure 1 - Diagram of individuals included in the study. Belo Horizonte, Brazil, 2015-2018.



ART: antiretroviral drug. Source: Authors.

The median age of individuals was 33 years (interquartile range - IQR=26-40). Most were male (81.8%), black or

brown skin color/ethnicity (71.4%), and had ten years of schooling or more (75.8%). Regarding clinical characteristics, most individuals started cART without clinical AIDS-defining conditions (79.0%), with a viral load ≤ 100,000 copies/mL (66.1%), TCD4 lymphocyte count > 200 cells/mm3 (66.1%) and used EFV-based regimen (67.2%). The characteristics of the study population are described in Table 1.

Table 1 - Characteristics of individuals included in the study. Belo Horizonte, Brazil, 2015-2018 (n=433).

Characteristics	n	%
Sex		
Male	354	81.8
Female	79	18.2
Age (years) [a]		
≤ 33	229	52.9
> 33	204	47.1
Age (years)		
16-19	18	4.2
20-34	235	54.3
35-49	133	30.7
50-68	47	10.9
Marital status		
Single/divorced/widowed	348	80.4
Married/ stable union	85	19.6
Skin color/ethnicity		
Brown	210	48.5
White	103	23.8
Black	99	22.9
Asian	14	3.2
Indigenous	3	0.7
Missing data	4	0.9
Socioeconomic class [b]		
Low (DE)	64	14.8
Intermediate (C)	203	46.9
High (AB)	155	35.8
Missing data	11	2.5
Educational level (years of formal education)		
≤ 9	104	24.0
10-12	171	39.5
13+	157	36.3
Missing data	1	0.2
Health insurance		
No	316	73.0
Yes	117	27.0
Employed		
No	176	40.6
Yes	257	59.4
Municipality of residence		
Belo Horizonte	384	88.7
Others	49	11.3
Smoking		
Non-smoker	213	49.2
Current smoker	117	27.0
Former smoker	97	22.4
Missing data	6	1.4

Source: Authors.

Table 1 - Characteristics of individuals included in the study. Belo Horizonte, Brazil, 2015-2018 (n=433). (Continuation)

Characteristics	n	%
Current alcohol use		
No	148	34.2
Yes	282	65.1
Use of any illicit drug in lifetime		
No	222	51.3
Yes	210	48.5
Missing data	1	0.2
Comorbidities (at least once)		
No	269	62.1
Yes	156	36.0
Missing data	8	1.8
AIDS-defining illness at baseline [c]		
Asymptomatic (A)	281	64.9
Symptomatic conditions (B)	61	14.1
AIDS-defining conditions	86	19.9
Missing data	5	1.2
Risk/exposure category		
Men who have sex with men	224	51.7
Heterosexual men	77	17.8
Heterosexual woman	54	12.5
Injecting drug use/others	22	5.1
Missing data	56	12.9
Antiretroviral regimen		
EFV/TDF/3TC	291	67.2
DTG/TDF/3TC	142	32.8
Changing cART		
No	393	90.8
Yes	40	9.2
Concomitant use of other non-ARV medications		
No	130	30.0
Yes	303	70.0
Adherence to cART at baseline [d]		
No	221	51.0
Yes	189	43.6
Missing data	23	5.3
Viral load at baseline (copies/mL)		
≤ 100,000	286	66.1
> 100,000	106	24.5
Missing data	41	9.5
CD4 count at baseline (cells/mm^3)		
< 200	111	25.6
200-500	157	36.3
> 500	129	29.8
Missing data	36	8.3

[a]: Categorized by its median value. [b]: Socioeconomic class measured using the Brazilian Association of Research Companies criteria;
[c]: Clinical classification of the stage of the disease evaluated using the adapted criteria of the Centers for Disease Control and Prevention;
[d]: Adherence to cART measured through the adapted 8-item Morisky Medication Adherence Scale.
Note: ARV: antiretroviral drug; cART: combination Antiretroviral Therapy; EFV/TDF/3TC – Efavirenz 600mg/Tenofovir disoproxil fumarate 300mg/Lamivudine 300mg; DTG/TDF/3TC – Dolutegravir 50mg/ Tenofovir disoproxil fumarate 300mg/Lamivudine 300mg. Source: Authors.

Two hundred seventeen (50.1%) of the 433 individuals had records of ADRs. At least one ADR record was observed in 60.8% of the individuals using the EFV/TDF/3TC regimen (n=177/291) and in 28.2% of the individuals using DTG/TDF/3TC (n=40/142). The use of other non-ARVs medications occurred in 303 individuals (70.0%), and the most

frequent was the use of antibacterials and antihistamines for systemic use, antimycobacterials, antimycotics, and psychoanaleptics. In 12 months, ARV switch were registered in 40 individuals (9.2%), and among these, 21 (52.5%) switched due to ADR.

ADR profile

In 12 months of follow-up, 695 ADRs were recorded, 604 (86.9%) in individuals using EFV/TDF/3TC and 91 (13.1%) in individuals using DTG/TDF/3TC. The mean number of ADRs per individual was 1.61 (standard deviation - SD=2.52), with a minimum of one and a maximum of 18. Seventy-three duplicated ADRs were identified; that means, the same ADR was reported more than once on different dates for the same individual. Duplicates were removed in the analysis of ADRs by antiretroviral regimen. Thus, 622 ADRs were recorded, and psychiatric disorders (34.4%), gastrointestinal disorders (30.9%), and nervous system (21.4%) disorders were the most frequent. Gastrointestinal disorders (20.4%) and nervous system disorders (16.9%) were more frequent among individuals using the DTG-based regimen, while psychiatric (48.5%), nervous system (37.5%), and gastrointestinal disorders (36.1%) were more frequent among individuals using the EFV-based regimen (Table 2). The complete description of ADRs according to PT and SOC MedDRA are attached as supplementary material (Table S1).

Table 2 - Adverse drug reactions classified according to SOC MedDRA recorded in clinical records within 12 months from the first dispensing of antiretrovirals, according to the antiretroviral regimen, 2015-2018, Belo Horizonte, Brazil.

Adverse drug reactions classified according to SOC MedDRA	All individuals n=433		EFV/TDF/3TC n=291		DTG/TDF/3TC n=142	
	n	%	n	%	n	%
Psychiatric disorders	149	34.4	140	48.1	9	6.3
Gastrointestinal disorders	134	30.9	105	36.1	29	20.4
Nervous system disorders	133	30.7	109	37.5	24	16.9
Skin and subcutaneous tissue disorders	77	17.8	71	24.4	6	4.2
General disorders and administration site conditions	42	9.7	39	13.4	3	2.1
Renal and urinary disorders	12	2.8	10	3.4	2	1.4
Metabolism and nutrition disorders	12	2.8	9	3.1	3	2.1
Eye disorders	11	2.5	9	3.1	2	1.4
Investigations	9	2.1	8	2.7	1	0.7
Respiratory, thoracic and mediastinal disorders	7	1.6	7	2.4	0	0.0
Musculoskeletal and connective tissue disorders	7	1.6	5	1.7	2	1.4
Ear and labyrinth disorders	6	1.4	5	1.7	1	0.7
Blood and lymphatic system disorders	6	1.4	5	1.7	1	0.7
Hepatobiliary disorders	5	1.2	5	1.7	0	0.0
Vascular disorders	4	0.9	4	1.4	0	0.0
Reproductive system and breast disorders	3	0.7	3	1.0	0	0.0
Immune system disorders	2	0.5	2	0.7	0	0.0
Injury, poisoning and procedural complications	1	0.2	1	0.3	0	0.0
Infections and infestations	1	0.2	1	0.3	0	0.0
Data not informed	1	0.2	1	0.3	0	0.0

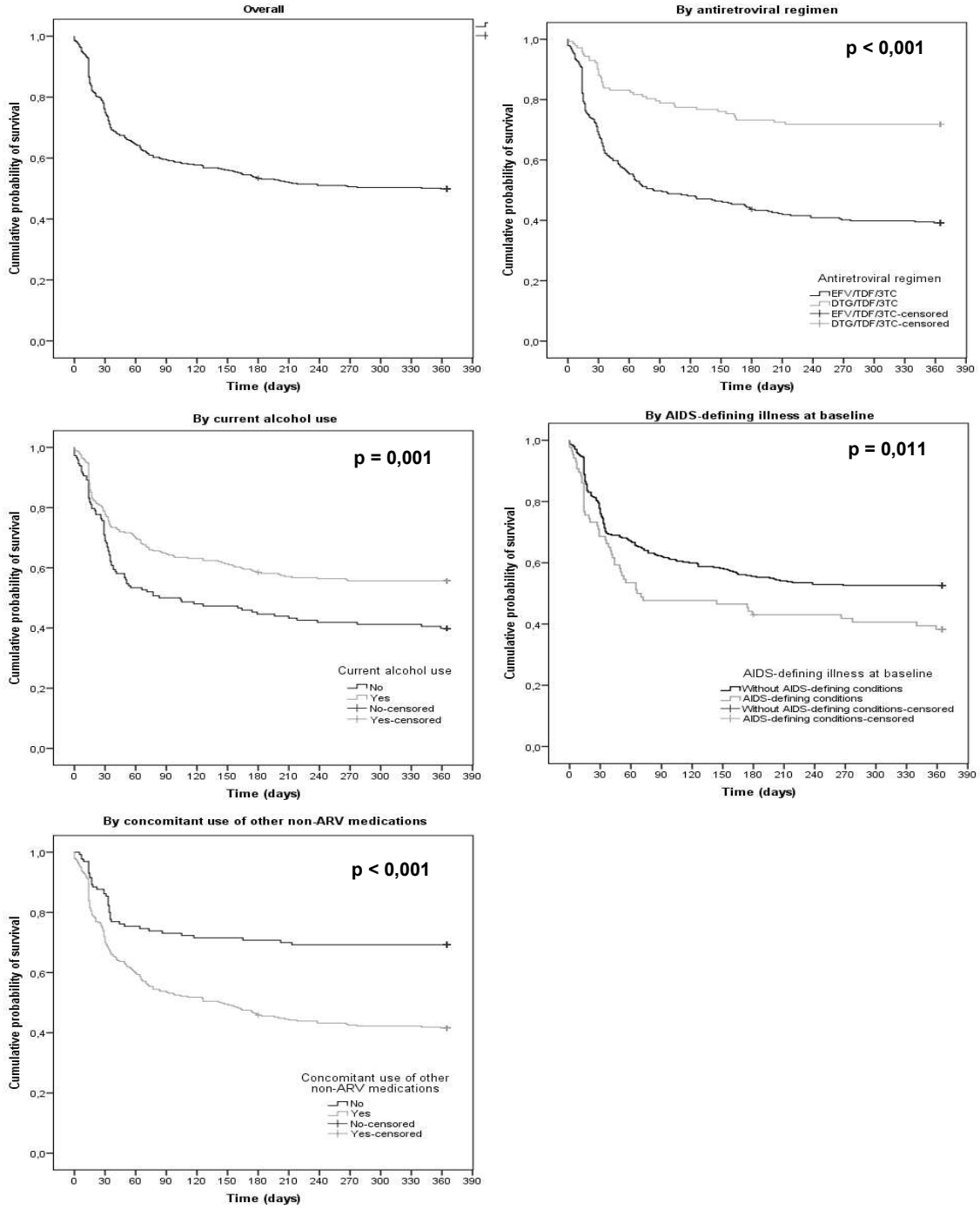
SOC Groups: System Organ Classes, Systemic Groups; EFV/TDF/3TC: Efavirenz 600mg/Tenofovir disoproxil fumarate 300mg/Lamivudine 300mg; DTG/TDF/3TC: Dolutegravir 50mg/ Tenofovir disoproxil fumarate 300mg/Lamivudine 300mg. Source: Authors.

Four deaths were recorded during the 12-month follow-up. One was due to bronchopneumonia, one due to septic shock during hospitalization, one due to suicide, and one due to lymphoma/pneumonia. There was no record of ADR-related deaths.

Survival time

The mean time to the first ADR was 210.6 days (95% confidence interval – 95% CI: 195.5-225.8). The probability of surviving without ADR at 30, 90, 180, and 365 days was 74.8%, 59.4%, 53.3%, and 49.9%, respectively. Individuals using DTG had a more extended time until the first ADR than those using EFV (p<0.001). Individuals who used alcohol had a more extended time until the occurrence of the first ADR than those who did not (p=0.001). Having AIDS-defining conditions at the onset of treatment (p=0.011) and the use of other non-ARVs (p<0.001) also had significant effects for a shorter time to the first ADR (Table 3). Kaplan-Meier survival curves with Log Rank tests are shown in Figure 2.

Figure 2 - Kaplan-Meier curves to estimate the probability of survival without adverse reactions after starting cART.



Source: Authors.

Table 2 - Average survival time until the occurrence of the first ADR, in days, of the study population and according to population characteristics, Belo Horizonte, Brazil, 2015-2018.

Characteristics	n	Event	Censored	Average survival time in days (95% CI)	p-value*
Overall	433	217	216	210.6 (195.5-225.8)	
Current alcohol use					0.001
No	148	89	59	179.2 (153.1-205.2)	
Yes	282	125	157	228.5 (210.0-247.0)	
AIDS-defining illness at baseline [a]					0.011
Without AIDS-defining conditions	342	162	180	218.2 (201.2-235.2)	
AIDS-defining conditions	86	53	33	177.0 (142.7-211.3)	
Antiretroviral regimen					<0.001
EFV/TDF/3TC	291	177	114	176.7 (158.2-195.1)	
DTG/TDF/3TC	142	40	102	280.2 (257.4-303.1)	
Concomitant use of other non-ARV medications					<0.001
No	130	40	90	266.6 (240.7-292.4)	
Yes	303	177	126	186.6 (168.7-204.6)	

*Log Rank Test. ARV: antiretroviral drug; EFV/TDF/3TC: Efavirenz 600mg/Tenofovir disoproxil fumarate 300mg/Lamivudine 300mg; DTG/TDF/3TC:Dolutegravir 50mg/ Tenofovir disoproxil fumarate 300mg/Lamivudine 300mg; 95% CI: 95% Confidence Intervals.
[a]: Clinical classification of the stage of the disease evaluated using the adapted criteria of the Centers for Disease Control and Prevention; Source: Authors.

In the multivariable Cox regression model, the use of other non-ARVs was a factor associated with an increased risk of ADR (Hazard Ratio - HR: 2.00; 95%CI 1.38-2.89), while the use of alcohol (HR: 0.64; 95%CI 0.49-0.85) and the DTG regimen (HR: 0.40; 95%CI 0.28-0.58) were factors associated with lower risk of ADR (Table 4).

Table 3 - Univariable and multivariable Cox proportional hazards models of factors associated with ADR in individuals living with HIV starting antiretroviral therapy, Belo Horizonte, Brazil, 2015-2018.

Characteristics	ADR n (%)*	Univariable Cox proportional hazards				Multivariable Cox proportional hazards		
		HR	95% CI		p-value	HR	95% CI	p-value
Sex								
Male	181 (83.4)	1.00						
Female	36 (16.6)	0.82	0.57	1.20	0.283			
Age (years) [a]								
≤ 33	114 (52.5)	1.00						
> 33	103 (47.5)	1.02	0.78	1.34	0.863			
Marital status								
Single/divorced/widowed	176 (81.1)	1.00						
Married/ stable union	41 (18.9)	0.96	0.68	1.35	0.811			
Skin color/ethnicity								
White	51 (23.5)	1.00						
Black	46 (21.2)	0.85	0.57	1.27	0.432			
Brown	108 (49.8)	0.98	0.70	1.36	0.887			
Asian/indigenous	10 (4.6)	1.26	0.64	2.48	0.504			
Socioeconomic class [b]								
High (AB)	72 (33.2)	1.00						
Low/Intermediate (CDE)	137 (63.2)	1.15	0.86	1.53	0.341			
Educational level (years of formal education)								
≤ 9	54 (24.9)	1.00						
10-12	84 (38.7)	0.92	0.65	1.30	0.761			
13+	78 (35.9)	0.96	0.68	1.40	0.834			

Table 4 - Univariable and multivariable Cox proportional hazards models of factors associated with ADR in individuals living with HIV starting antiretroviral therapy, Belo Horizonte, Brazil, 2015-2018. (Continuation)

Characteristics	ADR n (%)*	Univariable Cox proportional hazards				Multivariable Cox proportional hazards			
		HR	95% CI		p-value	HR	95% CI		p-value
Health insurance									
No	161 (74.2)	1.12	0.83	1.52	0.467				
Yes	56 (25.8)	1.00							
Employed									
No	94 (43.3)	1.00							
Yes	123 (56.7)	0.87	0.66	1.13	0.301				
Municipality of residence									
Belo Horizonte	194 (89.4)	1.00							
Others	23 (10.6)	0.95	0.62	1.46	0.804				
Current smoking									
No	160 (73.8)	1.00							
Yes	54 (24.9)	0.81	0.596	1.104	0.176				
Current alcohol use									
No	89 (41.0)	1.00				1.00			
Yes	125 (57.6)	0.64	0.49	0.84	0.001	0.64	0.49	0.85	0.002
Use of any illicit drug in lifetime									
No	110 (50.7)	1.00							
Yes	106 (48.8)	1.02	0.78	1.33	0.888				
Comorbidities (at least once)									
No	131 (60.4)	1.00							
Yes	82 (37.8)	1.18	0.89	1.55	0.236				
AIDS-defining illness at baseline [c]									
Without AIDS-defining conditions	162 (74.6)	1.00							
AIDS-defining conditions	53 (24.4)	1.49	1.09	2.03	0.011				
Risk/exposure category									
Men who have sex with men	121 (55.8)	1.00							
Heterosexual men	44 (20.3)	1.08	0.77	1.53	0.646				
Heterosexual woman	29 (13.4)	0.94	0.63	1.42	0.774				
Injecting drug use/others	6 (2.8)	0.41	0.18	0.93	0.033				
Antiretroviral regimen									
EFV/TDF/3TC	177 (81.6)	1.00				1.00			
DTG/TDF/3TC	40 (18.4)	0.35	0.25	0.49	<0.001	0.40	0.28	0.58	<0.001
Concomitant use of other non-ARV medications									
No	40 (18.4)	1.00				1.00			
Yes	177 (81.6)	2.31	1.63	3.25	<0.001	2.00	1.38	2.89	0.001
Adherence to cART at baseline [d]									
No	111 (51.2)	1.00				1.00			
Yes	91 (41.9)	0.99	0.75	1.30	0.921	0.98	0.77	1.34	0.915
Viral load at baseline (copies/mL)									
≤ 100,000	137 (63.1)	1.00							
> 100,000	61 (28.1)	1.28	0.95	1.73	0.105				
CD4 count at baseline (cells/mm^3)									
≤200	61 (28.1)	1.17	0.86	1.58	0.319				
>200	139 (64.1)	1.00							

[a]: Categorized by its median value. [b]: Socioeconomic class measured using the Brazilian Association of Research Companies criteria; [c]: Clinical classification of the stage of the disease evaluated using the adapted criteria of the Centers for Disease Control and Prevention; [d]: Adherence to cART measured through the adapted 8-item Morisky Medication Adherence Scale.

ADR: Adverse Drug Reactions; ARV: antiretroviral drug; cART: combination Antiretroviral Therapy EFV/TDF/3TC – Efavirenz 600mg/Tenofovir disoproxil fumarate 300mg/Lamivudine 300mg; DTG/TDF/3TC – Dolutegravir 50mg/ Tenofovir disoproxil fumarate 300mg/Lamivudine 300mg; HR: Hazard Ratio; 95% CI: 95% Confidence Intervals.

Multivariable Cox proportional hazards model: Concordance: 0.664 (Se=0.019); Likelihood Ratio Test: 67.6; 4df; p<0.001; Wald Test: 57.26; 4df; p<0.001; Score Test: 61.96; 4df; p<0.01. Source: Authors.

4. Discussion

This prospective cohort study with individuals who started treatment using a DTG-based or EFV-based regimen showed an incidence of ADR at 12 months of follow-up of 50.1%. ADRs occurred more frequently in individuals using the EFV-based regimen, and psychiatric disorders, gastrointestinal disorders, and nervous system disorders were the most frequently reported ADRs in the medical records. The mean time for individuals starting cART to develop the first ADR was 210.6 days, and there were significant differences regarding the time until the first ADR for clinical and behavioral characteristics. Factors associated with a higher risk of developing ADR were not using alcohol, EFV/TDF/3TC regimen, and concomitant use of other non-ARV medications.

The incidence of ADRs observed in this study was higher than that reported in other longitudinal studies held in Ethiopia (10.13% and 17.32%) (Kindie et al., 2017; Sherfa et al., 2021), South Africa (36.77%) (Masenyetse et al., 2015), and India (46.19%) (Chowta et al., 2018). These differences can be explained by evaluating different therapeutic regimens for the treatment of HIV in these studies since they were conducted in other countries, in which treatment recommendations are different from those adopted in Brazil. Some studies also differ by presenting different follow-up times. A prospective cohort study with 12 months of follow-up only with subjects using the EFV/TDF/3TC regimen conducted in China showed an ADRs incidence in 99.6% of subjects (Dai et al., 2020), a much higher number than observed in our study.

Most individuals with an ADR record were using the EFV/TDF/3TC regimen. The number of ADRs among individuals using the EFV-based regimen was much higher than that found among individuals under the DTG-based regimen. Results of a systematic review and meta-analysis comparing ARV regimens based on DTG and EFV suggest that treatment with DTG or low-dose EFV (400mg) is safer than treatment with 600mg EFV concerning adverse events and severe adverse events, besides causing less treatment discontinuation due to adverse events (Kanters et al., 2020).

Our study evidenced a more significant proportion of psychiatric disorders and nervous system disorders among individuals using the EFV-based regimen than individuals using DTG-based regimen. Many studies have reported neuropsychiatric events in individuals treated with DTG and EFV (Ford et al., 2015; Yombi, 2018; Hoffmann & Llibre, 2019; Fernández-Bargiela et al., 2020). However, treatment with DTG seems to be associated with fewer neuropsychiatric adverse events than EFV (Yombi, 2018; Kanters et al., 2020).

In this study, the mean time to the first ADR was different by ARV regimen, and individuals using DTG had a more extended time until the first ADR than those using EFV, which may be explained a by the higher proportion of neuropsychiatric events among individuals using EFV. As EFV has a high permeability in the blood-brain barrier, brain toxicity contributes to the higher occurrence of neuropsychiatric disorders, often reported in the first days of treatment (Gutiérrez-Valencia et al., 2009; Bertrand et al., 2021).

The results of previous studies are controversial regarding the effect of the ARV regimen on the time to develop ADRs. A retrospective cohort study carried out in Ethiopia with adults on cART found similar results to ours, and the baseline ARV regimen was related to differences in time for developing ADRs (Kibret et al., 2019). On the other hand, another retrospective study conducted in Ethiopia showed no association between the ARV regimen and the time to ADRs (Kindie et al., 2017). We could not identify studies in the literature comparing the survival time to developing ADR among individuals using regimens containing DTG and EFV, hindering comparisons with our results.

Individuals with AIDS-defining conditions at the start of treatment were more likely to have ADRs at any time than individuals without AIDS. In other studies, the advanced clinical classification of HIV infection at the onset of treatment was also associated with a shorter time for developing ADRs (Kindie et al., 2017; Sherfa et al., 2021). Individuals with AIDS-defining conditions or advanced clinical classification have compromised immunity and, therefore, an increased risk of opportunistic infections and the use of multiple medications. In turn, multidrug use is associated with a higher risk of ADRs

due to drug interactions (Mudigubba et al., 2018; Sherfa et al., 2021).

The concomitant use of other medications with cART was associated with a higher risk of ADRs at any time. This result is per the literature (Mudigubba et al., 2018; Siefried et al., 2018) since individuals on cART who use other medications have an increased risk of drug interactions and, thus, a higher risk of ADRs.

Alcohol use was associated with a lower risk of ADRs, which may be explained by the fact that it competes with drugs for binding to cytochrome enzymes. Ethanol can alter the metabolism of ARVs, which reduces the plasma concentration of ARVs (Kumar et al., 2015) and, consequently, the drug's possible adverse reactions in a usual concentration in the treatment of HIV can be reduced as well. Also, alcohol can cause acute body toxicities, such as headache and nausea, which usually occur after consuming the substance (Le Daré et al., 2019). Some of these symptoms are similar to the ADRs of ARVs, so some individuals who consume alcohol can attribute symptoms that would be ADRs to the alcohol effects, which, consequently, can lead to a lower number of ADRs reported to health professionals than the reality.

The DTG/TDF/3TC regimen was associated with a lower risk of ADRs than EFV/TDF/3TC regimen. This finding is in agreement with the literature (Nickel et al., 2021) since a systematic review study that compared the efficacy, safety, and durability of DTG against other ARVs in treatment-naive individuals showed that individuals in treatment with DTG have a lower risk of having ADRs (OR=0.6; 95%CI 0.3-0.9) than individuals on EFV treatment.

There was no association between adherence to cART and the presence of ADRs. Adherence was maintained in the final model due to clinical relevance for the assessment of ADRs, as causality was not evaluated. The occurrence of ADRs is associated with a lower chance of adherence (Carvalho et al., 2019; Cardoso et al., 2019). Non-adherence is not a predictor of ADRs, but a probable consequence of them.

cART's toxicity is a critical issue in managing the treatment of people living with HIV (Kibret et al., 2019). Individuals undergoing treatment with factors associated with ADRs described in this study should be monitored and periodically evaluated to verify the incidence of ADRs, especially very severe reactions that disable the performance of daily tasks. Thus, close monitoring and early detection of adverse events allows managing the treatment, which includes dose adjustment or change of a drug or regimen, and possibly preventing the treatment from being discontinued by the individual without medical advice.

The study's limitations are related to the use of secondary data from clinical records, which were not registered for the research, and, therefore, there is no record of aspects such as severity, causality, and duration of ADRs, limiting the assessment of these characteristics. Also, the information in the medical record usually evolves in medical appointments, which can take place over a longer time, which implies a possible overestimation of the time to developing ADRs. The main strengths of this study are the quality of data collection and robust statistical analysis to assess the time to ADRs development and associated factors. Furthermore, observational studies comparing the safety of EFV and DTG-based regimens are scarce in the literature, highlighting the originality of this study. Another strength is that ADRs were classified according to MedDRA, which facilitates comparing results with other national and international studies.

5. Conclusion

In conclusion, the DTG-based regimen had a better safety profile than the EFV-based regimen at 12 months of treatment. The mean time to develop the first ADR was 210.6 days. Behavioral (no alcohol use) and clinical (EFV-based regimen and concomitant use of other non-ARV medications) factors were associated with the incidence of ADRs and should be monitored when managing the treatment of individuals living with HIV.

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Conflicts of interest

The authors declare no conflict of interest.

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Table S1 - Complete description of adverse drug reactions classified according to PT and SOC MedDRA recorded in clinical records within 12 months from the first dispensing of antiretrovirals, according to the antiretroviral regimen, 2015-2018, Belo Horizonte, Brazil.

Adverse drug reactions classified according to PT and SOC MedDRA	All individuals n=433		EFV/TDF/3TC n=291		DTG/TDF/3TC n=142	
	n	%	n	%	n	%
Psychiatric disorders	**149**	**34.4**	**140**	**48.1**	**9**	**6.3**
Insomnia	41	9.5	36	12.4	5	3.5
Nightmare	35	8.1	34	11.7	1	0.7
Abnormal dreams	13	3.0	13	4.5	0	0.0
Anxiety	7	1.6	6	2.1	1	0.7
Sleep disorder	7	1.6	6	2.1	1	0.7
Irritability	5	1.2	4	1.4	1	0.7
Depressed mood	4	0.9	4	1.4	0	0.0
Listless	3	0.7	3	1.0	0	0.0
Libido decreased	3	0.7	3	1.0	0	0.0
Hallucination	3	0.7	3	1.0	0	0.0
Agitation	2	0.5	2	0.7	0	0.0
Panic attack	2	0.5	2	0.7	0	0.0
Suicidal ideation	2	0.5	2	0.7	0	0.0
Phonophobia	2	0.5	2	0.7	0	0.0
Poor quality sleep	2	0.5	2	0.7	0	0.0
Mood altered	2	0.5	2	0.7	0	0.0
Apathy	2	0.5	2	0.7	0	0.0
Loss of libido	1	0.2	1	0.3	0	0.0
Confusional state	1	0.2	1	0.3	0	0.0
Neuropsychiatric symptoms	1	0.2	1	0.3	0	0.0
Claustrophobia	1	0.2	1	0.3	0	0.0
Attention deficit hyperactivity disorder	1	0.2	1	0.3	0	0.0
Middle insomnia	1	0.2	1	0.3	0	0.0
Premature ejaculation	1	0.2	1	0.3	0	0.0
Hallucination, visual	1	0.2	1	0.3	0	0.0
Bradyphrenia	1	0.2	1	0.3	0	0.0
Depression	1	0.2	1	0.3	0	0.0
Sleep terror	1	0.2	1	0.3	0	0.0
Mood swings	1	0.2	1	0.3	0	0.0
Antisocial behaviour	1	0.2	1	0.3	0	0.0
Nervousness	1	0.2	1	0.3	0	0.0
Gastrointestinal disorders	**134**	**30.9**	**105**	**36.1**	**29**	**20.4**
Nausea	45	10.4	35	12.0	10	7.0
Diarrhoea	34	7.9	28	9.6	6	4.2
Vomiting	20	4.6	17	5.8	3	2.1
Abdominal pain upper	11	2.5	8	2.7	3	2.1
Dyspepsia	9	2.1	6	2.1	3	2.1
Abdominal pain	3	0.7	1	0.3	2	1.4

Table S1 - Complete description of adverse drug reactions classified according to PT and SOC MedDRA recorded in clinical records within 12 months from the first dispensing of antiretrovirals, according to the antiretroviral regimen, 2015-2018, Belo Horizonte, Brazil. (Continuation)

Adverse drug reactions classified according to PT and SOC MedDRA	All individuals n=433		EFV/TDF/3TC n=291		DTG/TDF/3TC n=142	
	n	%	n	%	n	%
Retching	2	0.5	2	0.7	0	0.0
Epigastric discomfort	2	0.5	2	0.7	0	0.0
Constipation	2	0.5	2	0.7	0	0.0
Dry mouth	1	0.2	0	0.0	1	0.7
Salivary hypersecretion	1	0.2	1	0.3	0	0.0
Odynophagia	1	0.2	1	0.3	0	0.0
Aphthous ulcer	1	0.2	1	0.3	0	0.0
Haematochezia	1	0.2	0	0.0	1	0.7
Glossodynia	1	0.2	1	0.3	0	0.0
Nervous system disorders	**133**	**30.7**	**109**	**37.5**	**24**	**16.9**
Dizziness	50	11.5	45	15.5	5	3.5
Headache	35	8.1	23	7.9	12	8.5
Somnolence	21	4.8	18	6.2	3	2.1
Presyncope	9	2.1	9	3.1	0	0.0
Tremor	4	0.9	3	1.0	1	0.7
Taste disorder	2	0.5	2	0.7	0	0.0
Disturbance in attention	2	0.5	2	0.7	0	0.0
Paraesthesia	2	0.5	2	0.7	0	0.0
Amnesia	1	0.2	0	0.0	1	0.7
Hypoesthesia	1	0.2	1	0.3	0	0.0
Hypersomnia	1	0.2	1	0.3	0	0.0
Dysgeusia	1	0.2	0	0.0	1	0.7
Dizziness postural	1	0.2	0	0.0	1	0.7
Memory impairment	1	0.2	1	0.3	0	0.0
Paraesthesia oral	1	0.2	1	0.3	0	0.0
Neurological symptom	1	0.2	1	0.3	0	0.0
Skin and subcutaneous tissue disorders	**77**	**17.8**	**71**	**24.4**	**6**	**4.2**
Rash	24	5.5	24	8.2	0	0.0
Pruritus	12	2.8	11	3.8	1	0.7
Hyperhidrosis	8	1.8	8	2.7	0	0.0
Rash maculo-papular	6	1.4	6	2.1	0	0.0
Alopecia	5	1.2	5	1.7	0	0.0
Rash pruritic	4	0.9	3	1.0	1	0.7
Urticaria	4	0.9	3	1.0	1	0.7
Drug eruption	3	0.7	2	0.7	1	0.7
Skin injury	3	0.7	3	1.0	0	0.0
Erythema	3	0.7	2	0.7	1	0.7
Rash macular	2	0.5	2	0.7	0	0.0
Exfoliative rash	1	0.2	1	0.3	0	0.0
Dermatitis acneiform	1	0.2	0	0.0	1	0.7
Rash erythematous	1	0.2	1	0.3	0	0.0

Table S1 - Complete description of adverse drug reactions classified according to PT and SOC MedDRA recorded in clinical records within 12 months from the first dispensing of antiretrovirals, according to the antiretroviral regimen, 2015-2018, Belo Horizonte, Brazil. (Continuation)

Adverse drug reactions classified according to PT and SOC MedDRA	All individuals n=433		EFV/TDF/3TC n=291		DTG/TDF/3TC n=142	
	n	%	n	%	n	%
General disorders and administration site conditions	**42**	**9.7**	**39**	**13.4**	**3**	**2.1**
Asthenia	10	2.3	9	3.1	1	0.7
Pyrexia	7	1.6	6	2.1	1	0.7
Feeling drunk	6	1.4	6	2.1	0	0.0
Malaise	5	1.2	4	1.4	1	0.7
Pain	3	0.7	3	1.0	0	0.0
Fatigue	3	0.7	3	1.0	0	0.0
Feeling hot	2	0.5	2	0.7	0	0.0
Tenderness	1	0.2	1	0.3	0	0.0
Crying	1	0.2	1	0.3	0	0.0
Chills	1	0.2	1	0.3	0	0.0
Oedema peripheral	1	0.2	1	0.3	0	0.0
Chest pain	1	0.2	1	0.3	0	0.0
Feeling of body temperature change	1	0.2	1	0.3	0	0.0
Renal and urinary disorders	**12**	**2.8**	**10**	**3.4**	**2**	**1.4**
Renal impairment	2	0.5	2	0.7	0	0.0
Proteinuria	2	0.5	2	0.7	0	0.0
Chromaturia	2	0.5	2	0.7	0	0.0
Acute kidney injury	1	0.2	1	0.3	0	0.0
Choluria	1	0.2	1	0.3	0	0.0
Microalbuminuria	1	0.2	0	0.0	1	0.7
Albuminuria	1	0.2	0	0.0	1	0.7
Renal failure	1	0.2	1	0.3	0	0.0
Dysuria	1	0.2	1	0.3	0	0.0
Metabolism and nutrition disorders	**12**	**2.8**	**9**	**3.1**	**3**	**2.1**
Decreased appetite	10	2.3	8	2.7	2	1.4
Fat intolerance	1	0.2	0	0.0	1	0.7
Hypoglycaemia	1	0.2	1	0.3	0	0.0
Eye disorders	**11**	**2.5**	**9**	**3.1**	**2**	**1.4**
Photophobia	3	0.7	2	0.7	1	0.7
Vision blurred	2	0.5	2	0.7	0	0.0
Dry eye	1	0.2	1	0.3	0	0.0
Visual field defect	1	0.2	1	0.3	0	0.0
Eye pruritus	1	0.2	1	0.3	0	0.0
Diplopia	1	0.2	1	0.3	0	0.0
Blindness transient	1	0.2	1	0.3	0	0.0
Eyelid oedema	1	0.2	0	0.0	1	0.7
Investigations	**9**	**2.1**	**8**	**2.7**	**1**	**0.7**
Transaminases abnormal	2	0.5	2	0.7	0	0.0
Transaminases increased	2	0.5	2	0.7	0	0.0

Table S1 - Complete description of adverse drug reactions classified according to PT and SOC MedDRA recorded in clinical records within 12 months from the first dispensing of antiretrovirals, according to the antiretroviral regimen, 2015-2018, Belo Horizonte, Brazil. (Continuation)

Adverse drug reactions classified according to PT and SOC MedDRA	All individuals n=433		EFV/TDF/3TC n=291		DTG/TDF/3TC n=142	
	n	%	n	%	n	%
Blood creatinine abnormal	2	0.5	1	0.3	1	0.7
Hepatic enzyme abnormal	1	0.2	1	0.3	0	0.0
Albumin urine	1	0.2	1	0.3	0	0.0
Blood bilirubin increased	1	0.2	1	0.3	0	0.0
Respiratory, thoracic and mediastinal disorders	**7**	**1.6**	**7**	**2.4**	**0**	**0.0**
Cough	4	0.9	4	1.4	0	0.0
Dyspnoea	3	0.7	3	1.0	0	0.0
Musculoskeletal and connective tissue disorders	**7**	**1.6**	**5**	**1.7**	**2**	**1.4**
Arthralgia	2	0.5	2	0.7	0	0.0
Myalgia	2	0.5	2	0.7	0	0.0
Muscular weakness	1	0.2	0	0.0	1	0.7
Pain in extremity	1	0.2	0	0.0	1	0.7
Muscle spasms	1	0.2	1	0.3	0	0.0
Ear and labyrinth disorders	**6**	**1.4**	**5**	**1.7**	**1**	**0.7**
Vertigo	5	1.2	4	1.4	1	0.7
Tinnitus	1	0.2	1	0.3	0	0.0
Blood and lymphatic system disorders	**6**	**1.4**	**5**	**1.7**	**1**	**0.7**
Neutropenia	2	0.5	2	0.7	0	0.0
Anaemia	1	0.2	0	0.0	1	0.7
Leukopenia	1	0.2	1	0.3	0	0.0
Normochromic normocytic anaemia	1	0.2	1	0.3	0	0.0
Haematotoxicity	1	0.2	1	0.3	0	0.0
Hepatobiliary disorders	**5**	**1.2**	**5**	**1.7**	**0**	**0.0**
Jaundice	3	0.7	3	1.0	0	0.0
Ocular icterus	1	0.2	1	0.3	0	0.0
Deficiency of bile secretion	1	0.2	1	0.3	0	0.0
Vascular disorders	**4**	**0.9**	**4**	**1.4**	**0**	**0.0**
Hyperaemia	3	0.7	3	1.0	0	0.0
Hypotension	1	0.2	1	0.3	0	0.0
Reproductive system and breast disorders	**3**	**0.7**	**3**	**1.0**	**0**	**0.0**
Gynaecomastia	2	0.5	2	0.7	0	0.0
Erectile dysfunction	1	0.2	1	0.3	0	0.0
Immune system disorders	**2**	**0.5**	**2**	**0.7**	**0**	**0.0**
Hypersensitivity	2	0.5	2	0.7	0	0.0
Injury, poisoning and procedural complications	**1**	**0.2**	**1**	**0.3**	**0**	**0.0**
Fall	1	0.2	1	0.3	0	0.0
Infections and infestations	**1**	**0.2**	**1**	**0.3**	**0**	**0.0**
Pustule	1	0.2	1	0.3	0	0.0
Data not informed	**1**	**0.2**	**1**	**0.3**	**0**	**0.0**
Data not informed	1	0.2	1	0.3	0	0.0

Note: PT: Preferred term; SOC Groups (System Organ Classes, Systemic Groups); EFV/TDF/3TC – Efavirenz 600mg/Tenofovir disoproxil fumarate 300mg/Lamivudine 300mg; DTG/TDF/3TC – Dolutegravir 50mg/ Tenofovir disoproxil fumarate 300mg/ Lamivudine 300mg.