Research, Society and Development, v. 11, n. 5, e43711528541, 2022
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v11i5.28541

Glucose, urea, and creatinine laboratory tests in people starting antiretroviral therapy with dolutegravir or efavirenz: a cohort study in Belo Horizonte, Brazil

Exames laboratoriais de glicose, ureia e creatinina em pessoas iniciando a terapia antirretroviral com dolutegravir ou efavirenz: estudo de coorte em Belo Horizonte, Brasil

Pruebas de laboratorio de glucosa, urea y creatinina en personas que inician terapia antirretroviral con dolutegravir o efavirenz: un estudio de cohorte en Belo Horizonte, Brasil

Received: 03/27/2022 | Reviewed: 04/04/2022 | Accept: 04/05/2022 | Published: 04/12/2022

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Abstract
Goal: In this study, we aimed to monitor the blood glucose, urea, and creatinine laboratory tests in treatment-naive individuals, initiating ART with an antiretroviral regimen containing EFV or DTG, searching for a contribution to the understanding of the safety of these drugs in use in the real world, followed up for 72 weeks. Methods: Cohort study with a follow-up of people living with HIV initiating antiretroviral therapy. Results: An increase in blood creatinine levels at 24 and 48 weeks and blood glucose levels at 48 weeks (p=0.017) was observed in the group using Dolutegravir. Those using Efavirenz evidenced an increase in creatinine levels at 48 weeks (p=0.007), blood glucose levels at 72 weeks (p=0.009), and urea levels at 48 weeks (p=0.023). Being male (p=0.044) and having more than 13 schooling years (0.044) explained the change in creatinine levels. Tobacco use (p=0.006), illicit drug use (p=0.009), and schooling greater than or equal to 13 study years (p=0.038) were independently associated with changes in urea levels. The therapeutic regimen with Efavirenz (OR=8.20; 95% CI=1.32-51.05; p=0.024) and schooling greater than or equal to 13 study years were independently associated with increased blood glucose concentration. Conclusions: The DTG regimen was associated with increased serum creatinine levels for up to 42 weeks and was transient and returning to the levels observed before the start of ART. The Efavirenz regimen was related to increased serum glucose levels, and the Dolutegravir therapy was the preferred regimen.
Keywords: HIV treatment; Antiretroviral therapy; Dolutegravir; Efavirenz; Laboratory tests.

Resumo
Objetivo: Monitorar os exames laboratoriais de glicemia, ureia e creatinina em indivíduos virgens de tratamento, iniciando TARV com esquema antirretroviral contendo EFV ou DTG, buscando contribuir para o entendimento da segurança desses medicamentos em uso no mundo real, acompanhados por 72 semanas. Metodologia: Estudo de coorte, com o acompanhamento de pessoas que vivem com HIV e iniciando terapia antirretroviral. Resultados: No grupo que usou dolutegravir, verificou-se aumento nos níveis de creatinina sanguínea em 24 e 48 semanas e glicose em 48 semanas (p=0,017). Naqueles que usaram efavirenz, verificou-se aumento nos níveis de creatinina em 48

semanas (p= 0,007), glicose em 72 semanas (p=0,009) e ureia 48 semanas (p=0,023). Pertencer ao gênero masculino (p=0,044) e apresentar mais que 13 anos de escolaridade (0,044) explicaram a alteração da creatinina. Uso de tabaco (p=0,006), uso de drogas ilícitas (p=0,009) e escolaridade maior ou igual a 13 anos de estudo (p=0,038) foram independentemente associados com as alterações nos níveis de ureia. O esquema terapêutico com efavirenz (OR = 8,20; 95% CI = 1,32-51,05; p=0,024) e escolaridade maior ou igual a 13 anos foram independentemente associados com o aumento na concentração de glicose. Conclusões: O esquema com DTG teve associação com o aumento na creatinina sérica por até 42 semanas, sendo transitório e retornando aos patamares observados antes do início da TARV. O esquema com efavirenz demonstrou estar relacionado com elevação nos níveis de glicose sérica, sendo preferencial a terapia com dolutegravir.
Palavras-chave: Tratamento HIV; Terapia antirretroviral combinada; Dolutegravir; Efavirenz; Exames laboratoriais.

Resumen
Objetivo: Monitorear los exámenes de laboratorio de glucosa, urea y creatinina en sangre en individuos vírgenes de tratamiento, que inician TARV con un régimen antirretroviral que contiene EFV o DTG, buscando contribuir a la comprensión de la seguridad de estos medicamentos en uso en el mundo real, seguidos durante 72 semanas. Metodología: Estudio de cohortes, con seguimiento de personas viviendo con VIH e iniciando terapia antirretroviral. Resultados: En el grupo que usó dolutegravir hubo aumento de los niveles de creatinina en sangre a las 24 y 48 semanas y de glucosa a las 48 semanas (p=0,017). En aquellos que usaban efavirenz, hubo un aumento en los niveles de creatinina a las 48 semanas (p=0,007), glucosa a las 72 semanas (p=0,009) y urea a las 48 semanas (p=0,023). Pertenecer al género masculino (p=0,044) y tener más de 13 años de escolaridad (0,044) explicaron la alteración de la creatinina. El consumo de tabaco (p=0,006), el consumo de drogas ilícitas (p=0,009) y la escolaridad mayor o igual a 13 años de escolaridad (p=0,038) se asociaron de forma independiente con cambios en los niveles de urea. El régimen terapéutico con efavirenz (OR = 8,20; IC 95% = 1,32-51,05; p=0,024) y la escolaridad mayor o igual a 13 años se asociaron de forma independiente con un aumento de la concentración de glucosa. Conclusiones: El régimen DTG se asoció con un aumento de la creatinina sérica hasta por 42 semanas, siendo transitorio y volviendo a los niveles observados antes del inicio del TARV. Se ha demostrado que el régimen de efavirenz está relacionado con un aumento en los niveles de glucosa sérica, prefiriéndose la terapia con dolutegravir.
Palabras clave: Tratamiento del VIH; Terapia antirretroviral combinada; Dolutegravir; Efavirenz; Pruebas de laboratorio.

1. Introduction

Human Immunodeficiency Virus (HIV) infection can cause biochemical and physiological changes in individuals, which lead to alterations in their laboratory tests, such as alterations in lipid metabolism, dyslipidemia, thrombocytopenia, anemia, and leukopenia (Redig & Berliner, 2013).

Antiretrovirals (ARVs) used in the treatment of HIV infection can cause adverse reactions and trigger metabolic changes, such as dyslipidemia, insulin resistance, glucose intolerance, changes in the function of organs such as kidneys, and liver. The use of ARVs may be associated with the redistribution of subcutaneous adipose tissue and increased visceral fat (Ronit et al., 2018).

Regarding renal function alterations, HIV-infected individuals may develop proteinuria, which may progress to HIV-associated nephropathy and impair renal function (Gardner et al., 2003). In this case, clinical conditions may vary from acute loss of renal function to chronic renal failure, both with the involvement of the glomeruli and renal tubules (Pinto et al., 2011; BRASIL, 2017; Nyende et al., 2020; Kaboré et al., 2019).

Monitoring laboratory tests is an essential part of care for people living with HIV (PLHIV), as it assists in the health team's decision-making regarding the proposed treatment and points to the need to change medications. Furthermore, it contributes to clinical follow-up, assists in the assessment of the individual's general health condition, indicates the effectiveness of antiretroviral therapy (ART), and assists in the search for comorbidities, when the frequency of request for tests recommended by the Ministry of Health (MS) is followed (BRASIL, 2018a).

In this setting, it is necessary to monitor renal function due to other risk factors for renal diseases, such as greater longevity of PLHIV and cumulative nephrotoxicity of ARVs (Pinto et al., 2011; BRASIL, 2017; Nyende et al., 2020; Joshi et al., 2018). Another aspect that deserves attention is that ART can lead to insulin resistance and abnormal glucose homeostasis,

contributing to the development of diabetes mellitus and cardiovascular disease (Tsuda et al., 2012).

In Brazil, the preferred initial regimen of ART for cases at the onset of treatment should follow the indication of the Clinical Protocols and Therapeutic Guidelines (PCDT) for the management of HIV infection in adults, which recommend the association of two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) analogs, using Lamivudine (3TC) and Tenofovir (TDF) associated with an Integrase Inhibitor (INI), Dolutegravir (DTG) (Pinto et al., 2011; BRASIL, 2017; Mclaughlin et al., 2018). Until 2017, Efavirenz (EFV), of the Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI) analogs class, was used in the first-line regimen, and was replaced by DTG (BRASIL, 2018a; Vieira et al., 2018).

The WHO recommended the DTG in first and second-line regimens for ART, which was also recommended by North American and European protocols (WHO, 2018). The DTG was incorporated into the Brazilian Unified Health System (SUS) in 2017 (BRASIL, 2018a) due to its higher safety profile, high potency, high genetic barrier, and low toxicity (Kolakowska et al., 2019; Dooley et al., 2020).

Given this protocol change, it is necessary to monitor through biochemical tests, follow-up on the HIV infection and the TCD4 lymphocyte count (LTCD4), assess the viral load (VL), and verify adherence to treatment (BRASIL, 2020).

In this study, we aimed to monitor the blood glucose, urea, and creatinine laboratory tests in treatment-naive individuals, initiating ART with an antiretroviral regimen containing EFV or DTG, searching for a contribution to the understanding of the safety of these drugs in use in the real world.

2. Methodology

2.1 Ethical aspects

This study is nested in the project titled “Effectiveness of Antiretroviral Therapy in people living with HIV, HIV/tuberculosis, HIV/leprosy, or HIV/visceral leishmaniasis (ECOART)”. The ECOART project was approved by the Research Ethics Committee of the Federal University of Minas Gerais under Ethical Assessment Presentation Certificate (CAAE) 31192914.3.0000.5149. All participants signed an informed consent form, and children under 18 signed an assent form.

2.2 Data collection

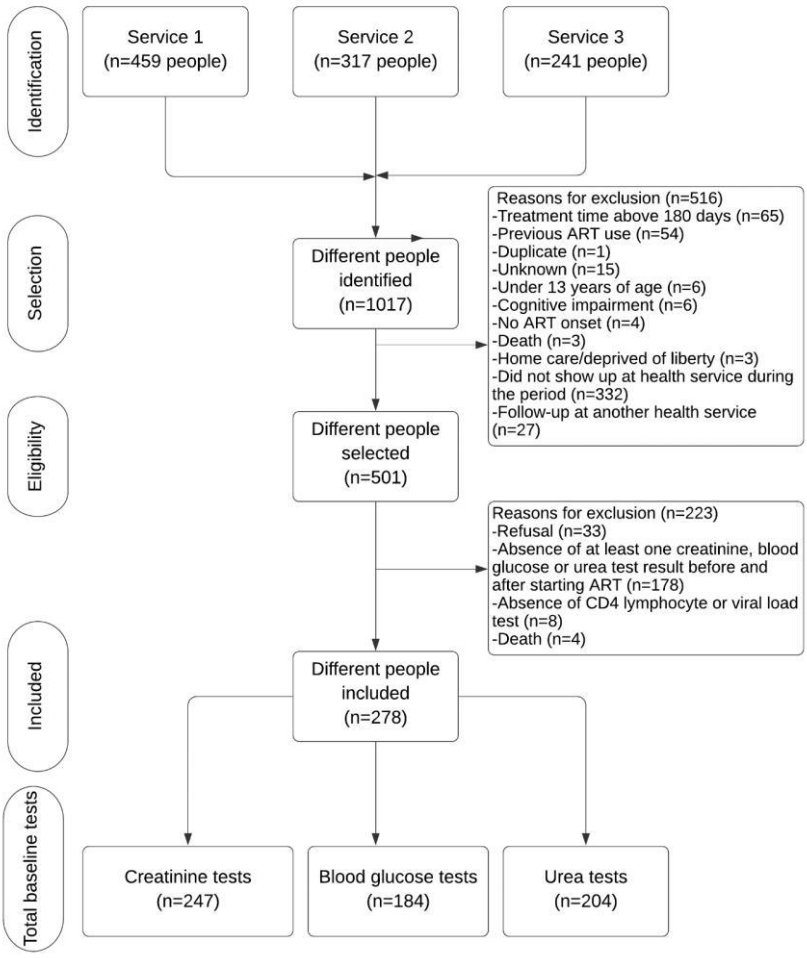
This work was a cohort study, which used data from the baseline interview of the ECOART Project (Mendes et al., 2018; Teixeira et al., 2020), data collected from clinical records, and information from the Laboratory Test Control System of the National Network for CD4/CD8 Lymphocyte Count and HIV Viral Load (SISCEL) and the Medication Logistic Control System (SICLOM). Participants were recruited from August 2015 to December 2018 in Belo Horizonte, Brazil.

The results of the blood glucose, urea, and creatinine laboratory tests were collected from the clinical records, according to the time of use of ARVs, at baseline (before starting ART) and up to 24, 48, and 72 weeks after starting ART. The VL and TCD4 exams were collected before starting ART.

The methods used in the laboratory tests performed by the SUS were the enzymatic colorimetric method for blood glucose measurements (mg/dL), the kinetic method for creatinine measurements (mg/dL), and the ultraviolet enzymatic method for urea measurements in mg/dL (Cysne et al., 2016).

A total of 1,017 people were selected from three public services of specialized assistance in HIV/AIDS, responsible for providing ART to approximately 80% of PLHIV in Belo Horizonte, and 501 people remained after applying the eligibility criteria. Then, 278 people remained after applying the inclusion and exclusion criteria for this study, 247 with creatinine test results, 184 with blood glucose test results, and 204 with urea test results (Figure 1).

Figure 1: Flowchart of eligibility of people included in the study.



Source: Authors.

2.3 Statistical analysis

Pearson's Chi-Square and Fisher's Exact tests were performed for categorical variables and the Mann-Whitney test for continuous variables (non-normal evaluated by the Shapiro-Wilk test) to compare the variables against ART. The parametric Student's t-test was used to compare the means of the groups for the independent variables, and the same test was applied for paired samples for the dependent variables for data that met the assumptions of normal distribution. The nonparametric Mann-Whitney test was used for independent variables, and the paired Wilcoxon test was used for dependent variables for data with no normal distribution.

A regression model suitable for each variable was employed to assess the creatinine, blood glucose, and urea tests outcomes. Univariate and multivariate linear regression models were estimated to assess creatinine and urea levels. Logistic regression was used for the blood glucose variable, for which the glucose variable was categorized into ≤ 99 and > 100 mg/dL. Thus, a logistic regression model was estimated. Analyses were performed using R and Rstudio software (version 4.1.0), considering 20% significance for univariate analysis and 5% significance for multivariate analysis.

3. Results

Most patients followed-up in the cohort were men (82.7%), using an antiretroviral regimen with EFV (63%), non-smokers (72.30%), alcohol use in the last month (74.8%), with no reported comorbidity (80.5%), belonging to economic classes D and E (57.5%). Most (50.7%) reported using illicit drugs in their lives, such as marijuana, cocaine, or crack, and

were adherent to ART (83.4%).

The study participants mean age was 35 (SD=11.18) and 33.7 years (SD=10.64) for DTG and EFV regimens, respectively. At the onset of ART, the individuals had, respectively, a mean VL of 139915.10 (SD=332077.73) and 153787.10 (SD=453986.54) copies/mm3 for the therapeutic regimens with DTG and EFV. The mean LTCD4 count was 444.96 (SD=267.22) and 404.61 (SD=271.92) cells/mm3 in the respective therapeutic groups. More than 97% of individuals started ART with detectable VL, ≥ 50 copies/mm3 in both treatment regimens studied.

We found that the two groups studied were homogeneous, except for the variable LTCD4 count (Table 1). Thus, 15.53% started ART in an immunodeficient condition, with an LTCD4 count < 200 cells/mm3 in the DTG regimen, and 26.86% started ART with an LTCD4 count < 200 cells/mm3 in the EFV regimen, results with a statistically significant difference (p=0.042).

Table 1: Baseline characteristics of individuals included in the study regarding antiretroviral treatment (n = 278).

Variables	DTG [a]		EFV [b]		
	Mean (SD)	Median (Q1-Q3) [c]	Mean (SD)	Median (Q1-Q3)	
Age (years)	35 (11.18)	33 (27-40)	33.70 (10.64)	32 (26-39)	
VL before ART	139915.1 (332077.7)	25649 (5312-67162)	153787.1 (453986.54)	25202 (4462-105556)	
LTCD4 before ART	444.96 (267.22)	410 (257-628)	404.61 (271.92)	390 (169-556)	
	n	%	n	%	p-value
Sex					
Male	87	84.47	143	81.71	0.673
Female	16	15.53	32	18.29	
Age group (years)					
16-19	3	2.91	6	3.43	0.721
20-34	58	56.31	99	56.57	
35-49	27	26.21	52	29.71	
≥ 50	15				
Skin color					
White	26	25.24	55	31.43	0.139
Black	51	49.51	67	38.29	
Brown	19	18.45	46	26.29	
Other	7	6.8	7	4.0	
Schooling (years)					
Up to 9	22	21.36	39	22.29	0.222
10-12	29	28.16	65	37.14	
> 12	52	50.49	71	40.57	
Economic class [d]					
A, B	1	0.97	1	0.57	0.893
C	44	42.72	72	41.14	
D, E	58	56.31	102	58.29	
Tobacco use					
Yes	33	32.04	44	25.14	0.270
No	70	67.96	131	74.86	
Alcohol use in the last month					
No	18	17.48	52	29.71	0.333
Yes	85	82.52	123	70.29	
Comorbidity [e]					
No	88	85.44	136	77.71	0.157
Yes	15	14.56	39	22.29	
Illicit drug use [f]					
No	49	47.57	88	50.29	0.755
Yes	54	52.43	87	49.71	
ART adherence [g]					
No	13	12.62	33	18.86	0.236
Yes	90	87.38	142	81.14	
VL before ART [h]					
Undetectable	3	2.91	4	2.29	1
Detectable	100	97.09	171	97.71	
LT-CD4 before ART					

< 200 cel/mm^3	16	15.53	47	26.86	0.042*
≥ 200 cel/ mm^3	87	84.47	128	73.14	

* Significant chi-square test at 5%. [a] DTG: antiretroviral regimen containing dolutegravir 50 mg associated with lamivudine 300 mg (3TC) and tenofovir 300 mg (TDF); [b] EFV: antiretroviral regimen containing efavirenz 600 mg associated with lamivudine 300mg (3TC) and tenofovir 300mg (TDF); [c] Interquartile range; [d] Economic class: according to the Institute for Applied Economic Research. Class A (> 20 minimum wages); Class B (10-20 minimum wages); Class C (4-10 minimum wages); Class D (2-4 minimum wages), Class E (up to 2 minimum wages); [e] Comorbidities recorded at the first visit (diabetes mellitus, systemic arterial hypertension, dyslipidemia, anxiety/depression, or other); [f] Illicit drugs = marijuana, cocaine, crack; [g] Adherence: did the person stop taking antiretroviral drugs in the last 15 days? Yes: non-adherent. No: adherent; [h] Undetectable ≤ 50 copies/mm^3 Detectable > 50 copies/mm^3. Source: Authors.

The mean time to diagnosis was 99.53 (SD=212.81) and 58.04 weeks (SD=110.24) for people on DTG and EFV regimens, respectively. The mean values for creatinine, blood glucose, and urea tests at 72 weeks of ART use were 61.40 (SD=6.86), 58.65 (SD=7.64), and 62.26 mg/dL (SD=8.72) for people using the regimen with DTG, and 56.35 (SD=6.52); 56.99 (SD=6.82) and 55.25 mg/dL (SD=5.64) for the regimen containing EFV, respectively.

Comparison tests were used to verify possible differences between the results of the tests according to the time of use of ARV drugs, shown in tables 2 and 3, stratified by antiretroviral regimen at baseline, 24, 48, and 72 weeks of follow-up. Concerning the TDF+3TC+DTG regimen, we found that the mean results for creatinine at 24 and 48 weeks were higher than the results before starting ART, 1,016 mg/dL (SD=0,238; p<0,001) and 0,977 mg/dL (SD=0.201; p=0.012) (Table 2, comparison 6). The comparison between 72 weeks of follow-up and baseline returned no significant difference.

When compared to baseline values, mean blood glucose at 48 and 72 weeks was 92,205 mg/dL (SD=14,324; p=0.017) and 100,391 mg/dL (SD=47,782; p=0.019), respectively. No statistically significant differences (Table 2, comparisons 1 and 4) were observed regarding the other temporal blood glucose comparisons. The mean urea test values showed no statistically significant difference (Table 2).

Table 2: Mean (mg/dL) and median changes in creatinine, blood glucose and urea levels in individuals using the antiretroviral regimen tenofovir, lamivudine, dolutegravir at baseline, 24, 48 and 72 weeks, Belo Horizonte-MG (n = 278).

Test	Comparison	Time, mean (SD)	Time, mean (SD)	P-value
Creatinine	1	Baseline, 0.932 (0.201)	72 weeks, 0.975 (0.177)	0.211^W
(mg/dL)	2	24 weeks, 0.978 (0.161)	72 weeks, 0.987 (0.174)	1.000^W
	3	48 weeks, 0.958 (0.181)	72 weeks, 0.963 (0.172)	0.768^T
	4	Baseline, 0.936 (0.181)	48 weeks, 0.977 (0.201)	0.012*^{W}
	5	24 weeks, 1.02 (0.213)	48 weeks, 0.992 (0.201)	0.129^W
	6	Baseline, 0.943 (0.227)	24 weeks, 1.016 (0.238)	<0.001*^{W}
Blood glucose	1	Baseline, 96.261 (40.542)	72 weeks, 100.391 (47.782)	0.019*^{W}
(mg/dL)	2	24 weeks, 93.267 (25.558)	72 weeks, 93.133 (15.052)	0.932^W
	3	48 weeks, 94.273 (26.511)	72 weeks, 107.273 (67.81)	0.441^W
	4	Baseline, 91.614 (28.892)	48 weeks, 92.205 (14.324)	0.017*^{W}
	5	24 weeks, 87.962 (8.962)	48 weeks, 91.577 (7.021)	0.063^W
	6	Baseline, 88.314 (10.181)	24 weeks, 89.982 (14.172)	0.075^W
Urea	1	Baseline, 26.764 (6.795)	72 weeks, 26.321 (5.637)	0.950^W
(mg/dL)	2	24 weeks, 25.273 (9.715)	72 weeks, 27.009 (6.150)	0.398^W
	3	48 weeks, 27.333 (3.489)	72 weeks, 25.833 (5.366)	0.341^T
	4	Baseline, 30.994 (12.23)	48 weeks, 28.245 (7.544)	0.449^W
	5	24 weeks, 29.176 (8.589)	48 weeks, 27.432 (7.217)	0.626^W
	6	Baseline, 29.755 (11.953)	24 weeks, 27.94 (8.441)	0.428^W

SD: standard deviation; W: Paired Wilcoxon Test; T: paired t test; *statistically significant at 5%. Source: Authors.

We observed that the mean creatinine concentration at 48 weeks was higher than baseline (SD=0.198; p=0.007) for people adopting the TDF+3TC+EFV therapeutic regimen (Table 3, Comparison 4).

Table 3: Mean (mg/dL) and median variations in creatinine, blood glucose and urea values in individuals using the antiretroviral regimen tenofovir, lamivudine, efavirenz at baseline, 24, 48 and 72 weeks, Belo Horizonte-MG (n = 278).

Test	Comparison	Time, mean (SD)	Time, mean (SD)	P-value
Creatinine	1	Baseline, 0.883 (0.17)	72 weeks, 0.901 (0.192)	0.301[T]
(mg/dL)	2	24 weeks, 1.149 (1.748)	72 weeks, 0.911 (0.197)	0.298[T]
	3	48 weeks, 0.904 (0.191)	72 weeks, 0.898 (0.204)	0.871[W]
	4	Baseline, 0.89 (0.18)	48 weeks, 0.929 (0.198)	0.007*[T]
	5	24 weeks, 0.945 (0.219)	48 weeks, 0.937 (0.201)	0.543[T]
	6	Baseline, 0.887 (0.179)	24 weeks, 1.012 (1.075)	0.146[T]
Blood glucose	1	Baseline, 91.927 (15.206)	72 weeks, 96.439 (23.373)	0.009*[W]
(mg/dL)	2	24 weeks, 96.037 (10.998)	72 weeks, 96.519 (27.309)	0.764[W]
	3	48 weeks, 95.115 (12.904)	72 weeks, 98.654 (28.448)	0.103[W]
	4	Baseline, 92.397 (23.928)	48 weeks, 96.154 (27.602)	0.064[T]
	5	24 weeks, 96.68 (18.838)	48 weeks, 97.44 (32.905)	0.755[T]
	6	Baseline, 91.25 (22.84)	24 weeks, 94.025 (16.44)	0.095[T]
Urea	1	Baseline, 27.741 (11.118)	72 weeks, 27.976 (7.319)	0.961[W]
(mg/dL)	2	24 weeks, 26.568 (8.432)	72 weeks, 27.635 (7.564)	0.572[W]
	3	48 weeks, 28.71 (7.842)	72 weeks, 27.871 (7.728)	0.629[W]
	4	Baseline, 27.89 (8.276)	48 weeks, 28.487 (7.217)	0.485[T]
	5	24 weeks, 26.616 (6.949)	48 weeks, 28.421 (7.128)	0.023*[T]
	6	Baseline, 27.996 (8.911)	24 weeks, 27.211 (7.939)	0.268[T]

SD: standard deviation; W: Paired Wilcoxon Test; T: paired t test; *statistically significant at 5%. Source: Authors.

The mean blood glucose value at 72 weeks was higher (96,439 mg/dL; SD=23,373; p=0.009) than baseline (91,927 mg/dL; SD=15,206; p=0.009) (Table 3, comparison 1).

The mean urea result at 48 weeks was 28,421 mg/dL (SD=7,128; p=0,023), higher than that of 24 weeks (26,616 mg/dL; SD=6,949; p=0,023) (Table 3, comparison 5). We observed no statistically significant difference for the other urea comparisons.

Table 4 shows the univariate and multivariate analyses of laboratory tests. Analyzing the characteristics of the population and the creatinine test results, the final model of the linear regression showed that male individuals had increased creatinine values (p=0.044), while those with schooling time greater than or equal to 13 years showed a reduction (p=0.041) at 72 weeks of follow-up.

Regarding the urea test, the final linear regression model showed that people who use tobacco (p=0.006) and individuals with 13 or more schooling years (p=0.038) had lower urea results, while illicit drug users evidenced an increase in this test (p=0.009).

Logistic regression of blood glucose results showed that the likelihood of a respondent using a therapeutic regimen with EFV to report an altered result was 8.20 times greater (95% CI=1.32-51.05; p=0.024) than others. Respondents with 13 years of schooling or more were 10.13 times more likely to have an increased blood glucose level (95% CI=1.31-78.18; p=0.026).

The Variance Inflation Factor (VIF) analysis evidenced no multicollinearity between the variables in the final models for urea, creatinine, and blood glucose.

Table 4: Univariate and multivariate analysis for creatinine, urea, and blood glucose tests according to follow-up time at 72 weeks and characteristics of study participants (n = 278).

Creatinine - Linear Regression		**Univariate**			**Multivariate [a]**	
Variables	Estimate	95% CI	p	Estimate	95% CI	p
Intercept	0.68	0.01 (1.34)	0.046*	0.97	0.85 (1.08)	<0.001*
Age (years)	0.00	0.00 (0.01)	0.554			
Tobacco use (yes)	0.09	-0.01(0.18)	0.087			
Alcohol use (yes)	0.00	-0.10 (0.09)	0.922			
Illicit drug use in lifetime (yes)	-0.03	-0.12 (0.06)	0.496			
ART adherence (no)	0.03	-0.07 (0.14)	0.514			
Therapeutic regimen (EFV)	-0.06	-0.16 (0.05)	0.262	-0.08	-0.16 (0.010)	0.084
Treatment time (weeks)	0.00	-0.01 (0.01)	0.981			
Skin color (brown)	0.08	-0.03 (0.19)	0.141			
Skin color (black)	-0.04	-0.15 (0.08)	0.522			
Skin color (other)	0.02	-0.23 (0.20)	0.886			
Sex (male)	0.16	0.02 (0.30)	0.027*	0.12	0.00 (0.241)	0.044*
Schooling (10-12 years)	-0.10	-0.25 (0.05)	0.208			
Schooling ≥ 13 years	-0.07	-0.22 (0.08)	0.351	-0.10	-0.23 (0.023)	0.107
Economic class (C)	0.11	-0.31 (0.53)	0.597	-0.12	-0.024 (-0.05)	0.041*
Economic class (D and E)	0.17	-0.25 (0.60)	0.412			
Comorbidity (yes)	-0.06	-0.19 (0.06)	0.319			
LT-CD4 before ART (≤ 200cel/mm^3)	-0.01	-0.12 (0.10)	0.854			
VL before ART (undetectable)	-0.07	-0.39 (0.26)	0.674			
Diagnosis time (weeks)	0.00	0.00 (0.00)	0.602			
Urea - Linear Regression		**Univariate**			**Multivariate [b]**	
Variables	Estimate	95% CI	p	95% CI	Estimate	p
Intercept	20.32	-7.20 (47.84)	0.144	27.56	22.86 (32.26)	<0.001*
Age (years)	0.08	-0.30 (0.14)	0.474			
Tobacco use (yes)	-4.04	-8.65 (0.57)	0.084	-5.35	-9.08 (-1.63)	0.006*
Alcohol use (yes)	-1.66	-6.77 (4.45)	0.516			
Illicit drug use in lifetime (yes)	3.80	-0.74 (8.35)	0.099	4.79	1.23 (8.35)	0.009**
ART adherence (no)	0.51	-4.77 (5.79)	0.846			
Therapeutic regimen (EFV)	2.20	-3.59 (8.00)	0.447			
Treatment time (weeks)	0.15	-0.18 (0.48)	0.370			
Skin color (brown)	-0.38	-5.85 (5.09)	0.890			
Skin color (black)	-2.37	-8.17 (3.44)	0.415			
Skin color (other)	-5.06	-14.08 (3.95)	0.263			
Sex (male)	4.64	-3.75 (13.03)	0.271			
Schooling (10 a 12 years)	-8.69	-16.53 (-0.86)	0.031*	-3.78	-8.21(0.66)	0.093
Schooling ≥ 13 years	-7.86	-15.09 (-0.63)	0.034*	-4.71	-9.14 (-0.28)	0.038*
Economic class (D e E)	0.97	-4.10 (6.05)	0.700			
Comorbidity (yes)	-2.18	7.96 (3.60)	0.450			
LT-CD4 before ART (≤ 200cel/mm^3)	0.04	-13.57 (13.64)	0.996	2.79	-1.41 (6.98)	0.189
VL before ART (undetectable)	4.11	-1.13 (9.35)	0.121			
Diagnosis time (weeks)	0.00	-0.03 (0.03)	0.950			
Blood glucose – Logistic Regression		**Univariate**			**Multivariate [c]**	
Variables	Estimate	95% CI	p	OR	95% CI	p
Intercept	-4.46	-14.41 (4.15)	0.333	0.00	0.00 (0.10)	0.001*
Age (years)	-0.03	-0.13 (0.06)	0.512			
Tobacco use (yes)	0.72	-1.42 (2.99)	0.506			
Alcohol use (yes)	0.82	-1.32 (3.35)	0.478			
Illicit drug use in lifetime (yes)	1.78	-0.12 (4.19)	0.096	4.57	0.93 (22.57)	0.062
ART adherence (no)	0.32	-2.07 (2.50)	0.777			
Therapeutic regimen (EFV)	2.26	-0.06 (5.11)	0.077	8.20	1.32 (51.05)	0.024*
Treatment time (weeks)	-0.01	-0.14 (0.11)	0.843			
Skin color (brown)	-0.47	-2.84 (1.72)	0.675			
Skin color (black)	-2.90	-7.13 (0.07)	0.099			
Skin color (other)	-15.23	NA (229.83)	0.997			
Sex (male)	0.52	-2.31 (3.36)	0.707			
Schooling (10 a 12 years)	-1.30	-4.86 (2.14)	0.444	1.14	0.14 (13.63)	0.774
Schooling ≥ 13 years	1.14	-1.73 (4.18)	0.427	10.13	1.13 (78.18)	0.026*
Economic class (D e E)	0.56	-1.95 (3.30)	0.664			

Comorbidity (yes)	1.74	-0.62 (4.38)	0.157
LT-CD4 before ART (≤ 200cel/mm^3)	-17.07	NA (777.71)	0.997
VL before ART (undetectable)	0.84	-1.57 (3.84)	0.524
Diagnosis time (weeks)	0.00	-0.01 (0.00)	0.660

[a] $R^2 = 0.948$ / [b] $R^2 = 0.953$ / [c]Area under the curve ROC Blood glucose = 0,849; [*] statistically significant at 5%. Source: Authors.

4. Discussion

The characteristics of this population were similar to other studies and epidemiological bulletins, and most patients were male, young, self-declared non-white, with high schooling level, alcohol use in the last month, and adhered to the ART regimen (Minas Gerais, 2018; Milburn et al., 2017; BRASIL, 2018b).

HIV infection has become a chronic evolution clinical condition due to the benefits of using ART (Oliveira et al., 2011). However, the improved quality of life brought other concerns with chronic non-communicable diseases prevalent in the general population, such as diabetes and kidney disease (Castro et al., 2016).

In this context, the participation of the clinical analysis laboratory is of great relevance to monitoring possible metabolic changes and the biochemical profile of people living with HIV using ART. Monitoring renal function becomes highly relevant as antiretroviral drugs are of continuous use and not free of nephrotoxic potential, even when we know that most kidney diseases only manifest clinically when more than 50% of the kidneys' functions are compromised (Dusse et al., 2016).

This study showed that people using a therapeutic regimen containing DTG had a transient increase in creatinine values at 24 and 48 weeks of follow-up. This finding corroborates data in the literature since DTG can inhibit the Organic Cation Transporter 2 (OCT_2), which mediates the tubular secretion of creatinine in the proximal renal tubules (Kolakowska et al., 2019; Mclaughlin et al., 2018; Cattaneo et al., 2020). Other studies explain that this increase is not a consequence of the reduced renal blood flow or renal creatinine clearance, which is not being a nephrotoxic effect, but a finding attributable to the inhibition of OCT_2 (Mclaughlin et al., 2018; Cattaneo et al., 2020), which is not clinically significant since it does not reflect a change in glomerular filtration rate (BRASIL, 2015).

The serum creatinine results as a renal function marker should be considered with caution, as its concentration may vary according to sex, age, muscle mass, muscle metabolism, nutritional status, and hydration status (Peres et al., 2013).

The change in urea concentration was not associated with the therapeutic regimens studied, but the covariates tobacco use, illicit drug use, and high schooling level significantly impacted the urea test. A negative relationship with tobacco use was identified, conflicting with other studies on similar populations.

The influence of tobacco on biochemical parameters was associated with an increased serum urea concentration, which can be explained by the nephrotoxic effect of cigarettes, higher intraglomerular blood pressure, and the dysfunction of renal endothelial cells (Orth, 2004; Camargo et al., 2006).

We found a significant increase in urea concentration in people who reported using illicit drugs, which is in agreement with the report of another study, where the use of illicit drugs triggered rhabdomyolysis, with muscle protein degradation and the release of a pool of amino acids, and its catabolism into ammonia. Subsequently, it is converted into urea, which justifies the change observed in the laboratory test (Akkina et al., 2012).

This is the first report in Brazil associating the use of EFV with an increase in blood glucose concentration above 100 mg/dL. This finding entirely agrees with a cohort study carried out in South Africa, which associated the use of antiretroviral EFV with a higher risk of developing diabetes mellitus. In randomized clinical trials, researchers showed that the use of EFV in first-line regimens in low- and middle-income countries was associated with higher blood glucose, which corroborates the findings of this study (Erlandson et al., 2014; Martínez et al., 2003).

People with high schooling were approximately ten times more likely to develop changes in blood glucose levels. However, we found no studies showing this association. On the other hand, a Brazilian study carried out on health determinants discussed that social issues, such as the level of education, can have implications for people's health levels (Martínez et al., 2003).

In this sense, individuals with long years of schooling are believed to have better financial conditions and income, with access to more significant volumes of processed foods and caloric intake, allowing the development of metabolic syndromes, such as diabetes mellitus (Carrapato et al., 2017).

The limitations of this study include the number of missing data for laboratory tests, the low number of women in the population, and a reduced follow-up time. Regarding the renal function analysis, we did not identify any data on the glomerular filtration rate (GFR), which would be necessary to assess the kidneys' functioning accurately.

The main strengths were the novelty of the study in analyzing the impact of EFV and DTG on blood glucose, urea, and creatinine tests in Brazil, the high quality of data collection by the qualified team, robust statistical analyses, real-life study, comparing two antiretroviral regimens used in Brazil and other countries around the world.

5. Conclusion

The study results showed that the use of DTG was associated with increased serum creatinine for up to 42 weeks, which was transient and returned to pre-ART onset levels. Furthermore, the use of EFV increased the likelihood of obtaining an altered blood glucose result, i.e., greater than 100 mg/dL. For this reason, the therapeutic regimen containing DTG is safer for ART-naive patients initiating drug therapy against HIV infection.

Thus, the use of the therapeutic regimen containing dolutegravir showed greater safety for the patient, when compared to the therapeutic regimen containing efavirenz.

Other studies involving the use of efavirenz and dolutegravir can demonstrate its association with alteration of other laboratory parameters and therefore its safety to the patient.

Acknowledgments

We are grateful to all patients who kindly agreed to participate in the study.

Conflict of interest

The authors declare that there is no conflict of interest.

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