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Change in body mass index: A cohort of individuals using dolutegravir

Alterações no índice de massa corporal: Coorte em indivíduos em uso de dolutegravir

Alteración en el índice de masa corporal: Cohorte en personas que utilizan dolutegravir

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Abstract
Goal: To assess body mass index (BMI) changes in people living with HIV (PLHIV) and using antiretroviral therapy (ART) with dolutegravir (DTG) and its associated factors. Methods: Retrospective and prospective cohorts of PLHIV who started ART with DTG or used DTG after changing the therapeutic regimen, from Belo Horizonte, between February/2017 and March/2020. Data were gathered from clinical records of the Drug Logistics and Laboratory Test Control Systems. BMI changes were analyzed in the following week intervals 1-24(t_{24}), 25-48(t_{48}), 49-72(t_{73}), and 73-96(t_{96}) using the Wilcoxon test and generalized estimation equation (GEE) model, at 5% significance level. Results: A total of 614 individuals were included and average was 38.4 years old. Most were men (85.5%) and 52.3% had started ART with DTG. These individuals, and the immunosuppressed ones, showed significant increases in BMI when compared to those who used DTG after switching therapeutics or the non-immunosuppressed ones (p-value <0.05). After 96 weeks, individuals starting ART with DTG had a mean increase in BMI of 1.02 Kg/m^2, whereas those who used DTG after the therapeutic change had an increase of 0.56 Kg/m^2 (p<0.05). DTG use length, ART type, immune status, baseline BMI, and age were associated (p<0.05) with BMI increases. Conclusions: We observed an increase in BMI both in individuals starting ART with DTG use and those using it after changing the therapeutic regimen.
Keywords: Dolutegravir; Integrase inhibitor; Antiretroviral therapy; Body mass index; BMI.

Resumo
Objetivo: Avaliar alterações no índice de massa corporal (IMC) em pessoas vivendo com HIV (PVHIV) utilizando terapia antirretroviral (TARV) com dolutegravir (DTG) e seus fatores associados. Métodos: Coorte retrospectiva e prospectiva de PVHIV que iniciaram TARV com DTG ou utilizaram DTG após troca do regime terapêutico, em Belo Horizonte, de fevereiro/2017 a março/2020. Os dados foram obtidos de prontuários clínicos, do Sistemas Logístico de Medicamentos e de Controle de Exames Laboratoriais. A variação do IMC nos intervalos de 1-24(t_{24}), 25-48(t_{48}), 49-72(t_{73}) e 73-96(t_{96}) semanas foi analisada por meio do teste de Wilcoxon e do modelo de equações de estimações generalizadas (GEE), com nível de significância de 5%. Resultados: A idade média dos 614 indivíduos incluídos foi de 38,4 anos. A maioria era homem (85,5%) e 52,3% dos indivíduos iniciaram a TARV com DTG. Aumento significativo no IMC foi observado em indivíduos que iniciaram TARV com DTG ou imunossuprimidos em relação àqueles que fizeram uso de DTG após troca de esquemas terapêutico ou não imunossuprimidos (valor p<0,05). Em 96 semanas, o aumento médio no IMC dos indivíduos que iniciaram TARV com DTG foi de 1,02 Kg/m^2 e naqueles que fizeram uso de DTG após troca foi 0,56 Kg/m^2 (p<0,05). Tempo de uso do DTG, tipo de TARV, *status* imunológico, IMC inicial e idade foram associados (p<0,05) ao aumento no IMC. Conclusões: Observamos aumento no IMC tanto de indivíduos que iniciaram TARV com DTG quanto naqueles que utilizaram DTG após troca no esquema terapêutico.
Palavras-chave: Dolutegravir; Inibidor da integrase; Terapia antirretroviral; Índice de Massa Corporal; IMC.

Resumen
Objetivo: Evaluar los cambios en el índice de masa corporal (IMC) en personas que viven con el VIH (PVVIH) que usan terapia antirretroviral (TAR) con dolutegravir (DTG) y sus factores asociados. Métodos: Cohorte retrospectiva y prospectiva de PVVIH que iniciaron TARV con DTG o usaron DTG después de cambiar su régimen terapéutico, en Belo Horizonte, de febrero / 2017 a marzo / 2020. Los datos se obtuvieron de los registros clínicos de los sistemas de control de pruebas de laboratorio y logística de medicamentos. Se analizó la variación del IMC en los intervalos de 1-24 (t_{24}), 25-48 (t_{48}), 49-72 (t_{73}) y 73-96 (t_{96}) semanas mediante la prueba de Wilcoxon y el modelo de ecuación de estimación generalizada (GEE), con un nivel de significancia del 5%. Resultados: Se incluyeron 614 individuos con una edad mediana de 38,4 años. La mayoría fueron varones (85,5%) y el 52,3% de los individuos iniciaron TARV con DTG se observó un aumento significativo en el IMC en los individuos que iniciaron TARV con DTG o inmunosuprimidos en comparación con aquellos que usaron DTG después de cambiar los regímenes terapéuticos o no inmunosuprimidos (valor de p <0.05). A las 96 semanas, el aumento medio en el IMC de los individuos que iniciaron TARV con DTG fue de 1,02 kg / m^2 y en los que utilizaron DTG después del reemplazo fue de 0,56 kg / m^2 (p <0,05). La duración del uso de DTG, el tipo de TAR, el estado inmunológico, el IMC inicial y la edad se asociaron (p <0,05) con un aumento del IMC. Conclusiones: Observamos un aumento del IMC tanto en los individuos que iniciaron TARV con DTG como en los que usaron DTG después de cambiar el régimen terapéutico.
Palabras chave: Dolutegravir; Inhibidor de la integrasa; Terapia antirretroviral; Índice de masa corporal; IMC.

1. Introduction

The development and introduction of combination antiretroviral therapy (ART) have greatly improved the life expectancy of people living with HIV (PLHIV) by restoring immunity, delaying disease progression, and decreasing morbidity and mortality (Adam et al., 2017; Castelo Filho & Pott-Junior, 2016).

In 2017, the Clinical Protocol and Therapeutic Guidelines (PCDT), promulgated by the Brazilian Ministry of Health, recommended daily use of one 300 mg tenofovir (TDF) or 300 mg lamivudine (3TC) tablet, both nucleoside analogue reverse transcriptase (NRTI) inhibitors, associated to one 50 mg dolutegravir (DTG) tablet, an integrase inhibitor (INI), as a first-line regimen for HIV treatment (BRASIL, 2018).

ART promotes immune recovery and improves survival among individuals. Furthermore, it also contributes to body weight recovery among individuals with a low baseline body mass index - BMI (Obry-Roguet et al., 2018; Yuh et al., 2015). However, being overweight is a known risk factor for developing cardiovascular diseases and diabetes mellitus in a population in general and has been a growing concern among PLHIV (Debroy et al., 2019).

A clinical study has demonstrated that individuals using DTG have greater body weight gains than those taking other pharmacotherapeutic regimens (Eckard & McComsey, 2020). However, the effect of DTG on BMI is little explored in the literature. Little is known on the mechanisms by which DTG and other INI promote metabolic changes that lead to weight gains in individuals, but there is a hypothesis of an inflammatory action in adipose tissue from HIV infection and from ART itself (Lake, 2017).

This study aimed to longitudinally evaluate BMI changes in PLHIV under ART with therapeutic regimens containing DTG, from the beginning of treatment or after changing therapeutic regimen containing DTG, and its associated factors.

2. Methodology

A retrospective and prospective cohort study was performed enrolling individuals assisted at a specialized HIV service, from February 2017 to March 2020, in Belo Horizonte - MG, Brazil. This service is a reference for providing the general population with rapid diagnostic tests and laboratory tests for HIV and other sexually transmitted infections, in addition to monitoring and treating PLHIV linked to it. All individuals registered for care at that facility aged 18 years or over and had started ART with a therapeutic regimen containing DTG or started using it after changing the therapeutic regimen. We excluded individuals who, before starting ART with DTG or switching to regimens with DTG, had no records of weight, height, TCD4+ lymphocyte count, or viral load; individuals who had records of body weight for a period longer than six months before DTG

use (initially or after change); those who did not start clinical follow-up and/or treatment in the evaluated service center; those who used post-exposure prophylaxis before using DTG; people who performed bariatric surgery during the observational period; and all women who were pregnant or became pregnant during the research period. The follow-up started (time zero) from the first DTG dispensation registered in the Logistics System of Medicines (SICLOM) between February/2017 to March/2020. Data on weight, height, blood pressure, viral load, and TCD4+ lymphocyte count was collected from clinical records. From the beginning of DTG use, six sequential data on weight and blood pressure were collected from medical records during medical or pharmaceutical consultations, up to a maximum of 96 weeks. The SICLOM and Laboratory Test Control System (SISCEL) were used to collect data regarding the treatment regimen in use, treatment time, TCD4+ lymphocyte count, viral load, age, ethnic self-definition, sex, marital status, and education.

The dependent variable consisted of changes in body mass index (BMI). This index was calculated by dividing body weight in kilograms (kg) by height in meters squared (m^2). BMI changes during the follow-up period were estimated by subtracting the final BMI from the initial BMI mean values. These follow-up periods were divided into five weekly intervals, namely: initial (t0), 1 to 24 (t_{24}), 25 to 48 (t_{48}), 49 to 72 (t_{72}), and 73 to 96 (t_{96}). In the case of more than one record within the same interval, we considered the one with the longest time. BMI data were categorized into underweight (<18.5 kg/m^2), eutrophic (18.5≤x<25.0 kg/m^2), overweight (25≤x<30.0 kg/m^2), and obese (≥30 Kg/m^2), according to the World Health Organization (WHO, 2004). Sociodemographic (gender, age, skin color, education, marital status), clinical (weight, blood pressure, immune status (TCD4+), viral load) and pharmacotherapeutic (first regimen and time) traits were established as independent variables. Individuals with TCD4+ lymphocyte count less than 200 cells/ µL were considered immunosuppressed, and those whose value was greater than or equal to 200 cells/µL were not. Viral load (VL) was established in two categories: detectable viral load (above or equal to 50 copies/mL) and undetectable (below 50 copies/mL). Two categories for blood pressure were also established, namely: 1) systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg (hypertensive), and 2) systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg (normotensive).

Measures of central tendency were taken for the variable age, while frequency distribution was used for the other sociodemographic, clinical, pharmacotherapeutic variables. Uniformity between groups of individuals was compared by Pearson's chi-square test or Fisher's exact test. Data distribution was assessed using the Shapiro-Wilk test. In univariate analyses, regarding the ART regimen (starting or switching to regimens with DTG), immunological status (TCD4+ and viral load) and gender, Wilcoxon tests were performed to assess the BMI changes within the established periods. In multivariate analyses, using the Generalized Estimating Equation (GEE) model (Halekoh, Højsgaard, & Yan, 2006; Hubbard et al., 2010; Santos Pinto Guimarães, Naomi Hirakata, & Alegre, 2012), evaluations were performed between the averages of initial BMI variation (t_0) and those in the following weekly intervals: 1-24(t_{24}), 25-48(t_{48}), 49-72(t_{72}), and 73-96(t_{96}), considering age, age group, sex, skin color, education, marital status, ART, immune status, BMI category, and blood pressure. Multicollinearity analyses were performed in the models by the variance inflation factor (VIF). For model fit, the Wald test was used to establish the variables with statistical significance lower than 20%. After, only the variables with statistical significance lower than 5% were considered in the final model. BMI changes over time for the different groups (initial DTG use or DTG use after changing regimens) and interaction between the factors were evaluated. A first-order autoregressive covariance matrix was used to verify the relationship of the effects. To assess the most suitable covariance matrix for the model, the quasi-likelihood criterion under the corrected independence model (QIC) was used, which is a modification of the Akaike information criterion (AIC) for GEE analysis. The lower the QIC, the better the model fit (Cui, 2007). All analyses were performed using the R software version 4.0.2 and a significance level of 5%.

The study is part of the ECOART Project "Effectiveness of ART in PLHIV, HIV/tuberculosis, HIV/leprosy or HIV/visceral leishmaniasis" approved by the Research Ethics Committees of the *Universidade Federal Minas Gerais* - UFMG

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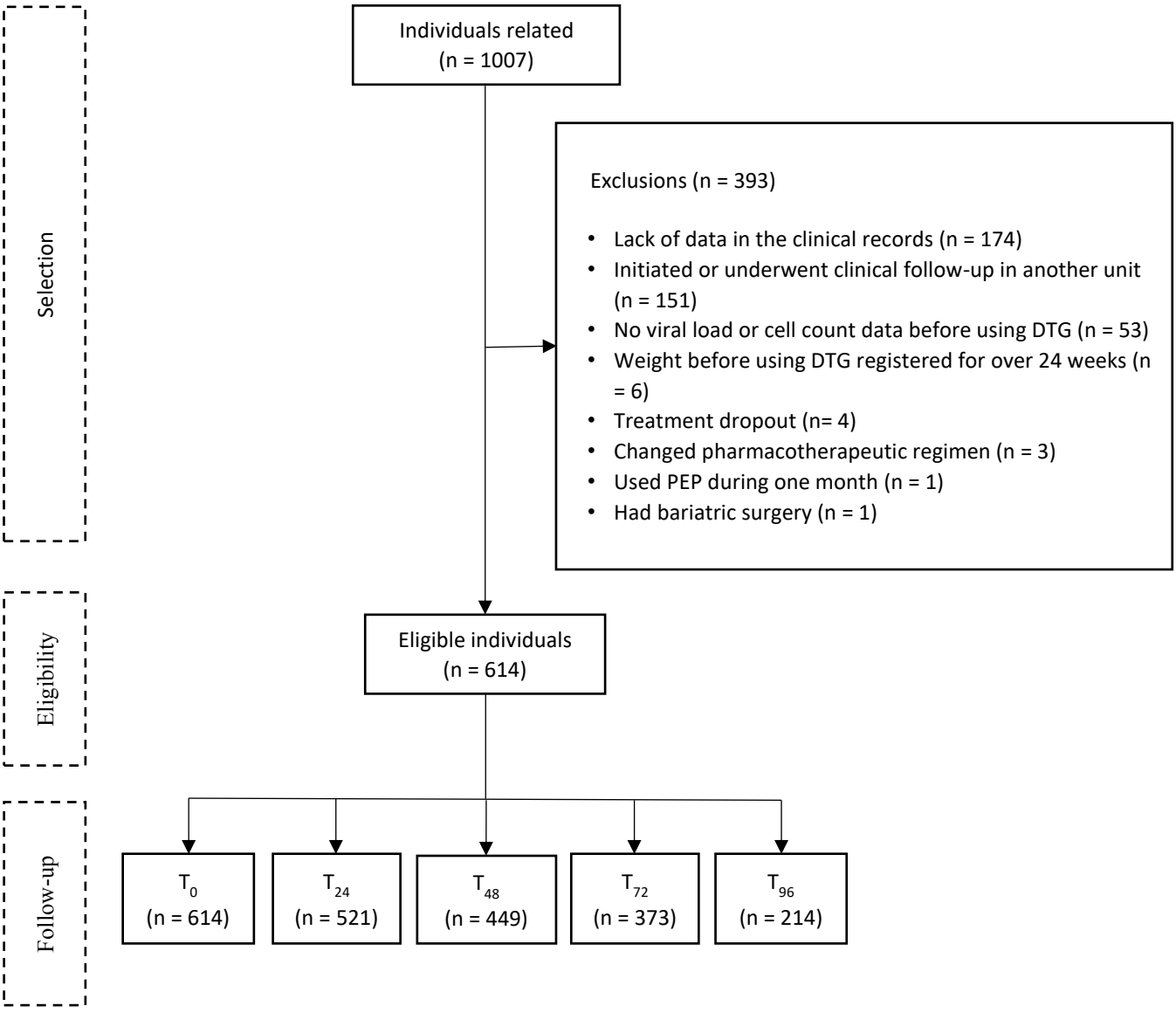
3. Results

In October/2019 (t_0), 1,007 individuals assisted in the evaluated service were using DTG, of which 614 met the eligibility criteria and were then included in the study (Figure 1).

Figure 1: Diagram of inclusions and exclusions of individuals in the study.



DTG: dolutegravir; PEP: Post-exposure prophylaxis; T: Time in weeks. Source: Authors.

Table 1 shows that 52.3% of the individuals started ART with DTG use in a pharmacotherapeutic regimen DTG + TDF/3TC, whereas the other 47.7% started without DTG use in other regimens, of which the association of efavirenz (EFV) /TDF/3TC predominated (26.1%). The average age of the individuals was 38.4 years, with a predominance of people between 21 and 40 years old (61.3%). The majority were men (85.8%), mixed skin color (45.8%), whether single, widowed or divorced (77.7%), and with 12 years of schooling or more (44.1%). Regarding clinical traits, 86.2% of the individuals had TCD4+ lymphocyte count ≥200 cells/ μL and 54.6% viral load ≥50 copies/mL. Among individuals who started ART with DTG use, a

higher percentage (98.1%) had a detectable viral load (≥50 copies/mL). Conversely, among those who used DTG after switching regimens, a higher percentage (93.2%) had an undetectable viral load (<50 copies/mL). Most individuals (79.0%) had blood pressure values within normal limits and BMI within the normal category (54.6%).

Table 1: Characteristics of people living with HIV followed up in a reference service in Belo Horizonte city on antiretroviral therapy with initial use of dolutegravir or after changing therapeutic regimens (n=614).

		PVHIV on ART		
	Total population (N = 614) n (%)	**DTG after change (N = 293) n (%)**	**initial use of DTG (N = 321) n (%)**	***p*-value**
Age*				< 0.001
Median (Q_1-Q_3)	35.7 (28.3-46.7)	42.1 (34.7-52.6)	30.2 (25.8-38.1)	
Age range				< 0.001
18-20	11 (1.8)	0 (0)	11 (3.4)	
21-30	197 (32.1)	44 (15)	153 (47.7)	
31-40	179 (29.2)	90 (30.7)	89 (27.7)	
41-50	113 (18.4)	72 (24.6)	41 (12.8)	
51-60	74 (12.1)	58 (19.8)	16 (5)	
61-70	33 (5.4)	23 (7.8)	10 (3.1)	
71-80	6 (1)	5 (1.7)	1 (0.3)	
81-90	1 (0.2)	1 (0.3)	0 (0)	
Sex				< 0.001
Female	87 (14.2)	64 (21.8)	23 (7.2)	
Male	527 (85.8)	229 (78.2)	298 (92.8)	
Skin color				0.088
White	229 (37.3)	115 (39.2)	114 (35.5)	
Brown	281 (45.8)	121 (41.3)	160 (49.8)	
Black	62 (10.1)	31 (10.6)	31 (9.7)	
Non-informed / others	42 (6.8)	26 (8.9)	16 (5)	
Marital status				< 0.001
With spouse	68 (11.1)	38 (13)	30 (9.3)	
Without spouse	477 (77.7)	205 (70)	272 (84.7)	
Non-informed	69 (11.2)	50 (17.1)	19 (5.9)	
Schooling time**				< 0.001
1 to 3 years	13 (2.1)	11 (3.8)	2 (0.6)	
4 to 7 years	46 (7.5)	30 (10.2)	16 (5)	
8 to 11 years	188 (30.6)	92 (31.4)	96 (29.9)	
12 or more	271 (44.1)	106 (36.2)	165 (51.4)	
Non-informed	96 (15.6)	54 (18.4)	42 (13.1)	
BMI category				0.005
Underweight	42 (6.8)	13 (4.4)	29 (9)	
Eutrophic	335 (54.6)	149 (50.9)	186 (57.9)	
Overweight	179 (29.2)	95 (32.4)	84 (26.2)	
Obese	58 (9.4)	36 (12.3)	22 (6.9)	
Blood pressure				0.544
Hypertensive	129 (21)	58 (19.8)	71 (22.1)	
Normotensive	485 (79)	235 (80.2)	250 (77.9)	

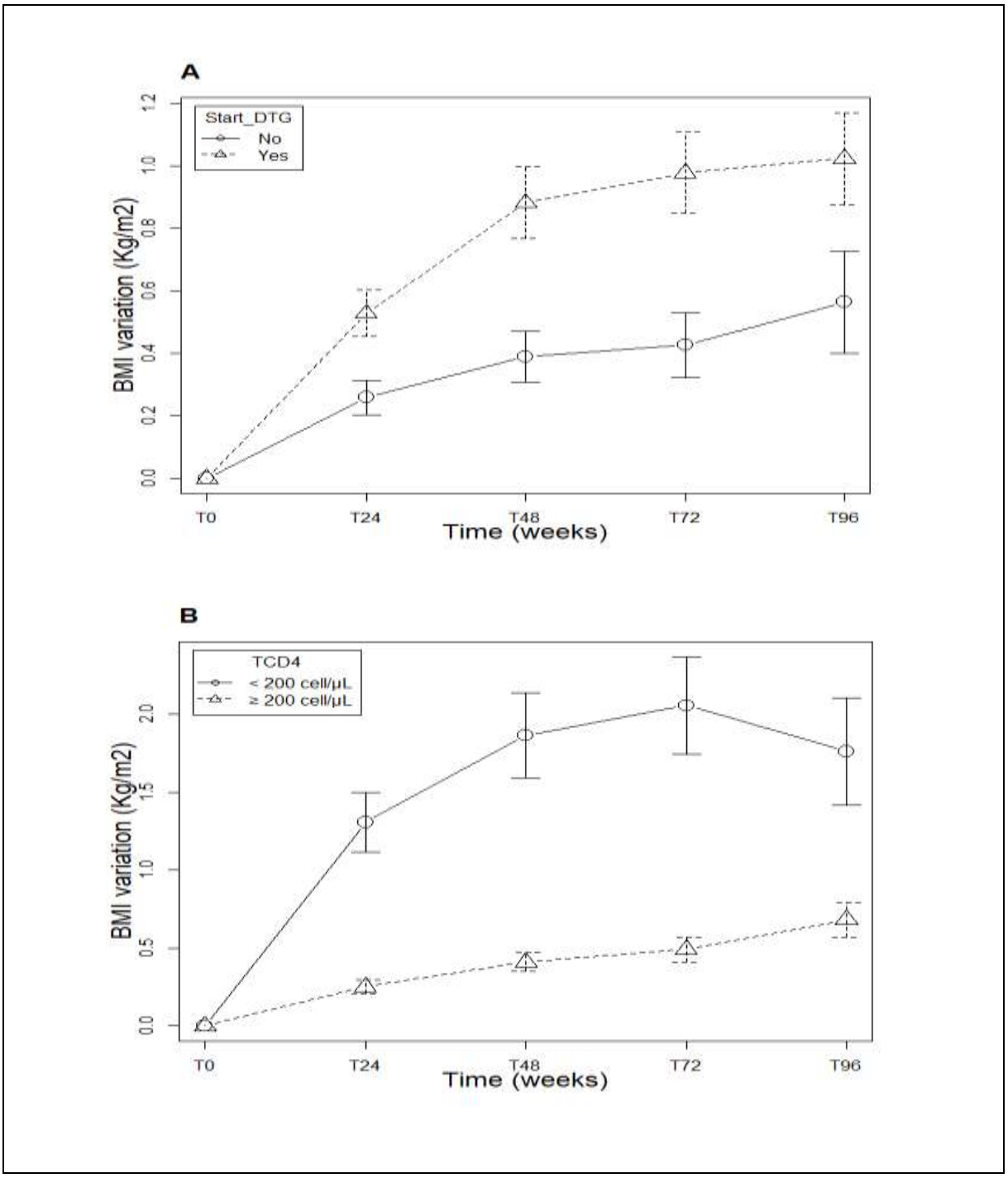
ART**				< 0.001
DTG+TDF+3TC	321 (52.3)	0 (0)	321 (100)	
EFV+TDF+3TC	160 (26.1)	160 (54.6)	0 (0)	
RAL + Others	30 (4.9)	30 (10.2)	0 (0)	
Others	103 (16.8)	103 (35.2)	0 (0)	
TCD4+ cell count				< 0.001
< 200 cells/ µL	85 (13.8)	9 (3.1)	76 (23.7)	
≥ 200 cells/ µL	529 (86.2)	284 (96.9)	245 (76.3)	
Viral load (RNA-HIV-1)				< 0.001
< 50 copies/mL	279 (45.4)	273 (93.2)	6 (1.9)	
≥ 50 copies/mL	335 (54.6)	20 (6.8)	315 (98.1)	

* Age: Median (Interquartile range); ** Fisher's exact test
ART: Antiretroviral therapy; DTG: Dolutegravir; EFV: Efavirenz; RAL: Raltegravir; 3TC: Lamivudine; BMI: Body mass index.
Source: Authors.

Regarding BMI, higher percentages of underweight and eutrophic individuals (66.9%) were found in the group that started ART with DTG use. Over time, the proportions of overweight and obese individuals increased, especially among those who started ART with GTD use. After 48 and 96 weeks, 4.3 and 6.8% increases in the composition of the groups were observed according to BMI, respectively.

Univariate analyses showed that individuals who started ART using DTG generally had greater BMI increases than did those who used DTG after switching therapies (p-value <0.05), in all periods evaluated (Figure 2, Table 2). At week 96, BMI showed significant gains of 1.02 and 0.56 kg/m^2 for individuals using DTG initially and after regimen switch, respectively. Women had average BMI increases higher than did men (1.23 versus 1.00 kg/m^2). BMI also increased in immunosuppressed individuals who, regardless of the pharmacotherapeutic regimen, had a greater change in BMI when compared to non-immunosuppressed individuals (p-value ≤0.001) (Figure 2, Table 2). BMI changes in immunosuppressed individuals with detectable viral load (≥50 copies/mL) were like that of individuals starting ART using DTG. On average, immunosuppressed individuals had a BMI gain of 1.76 kg/m^2 within 96 weeks. Although women who started ART using DTG also had greater BMI gains compared to those who used it after switching therapies, this difference was not statistically significant (p-value >0.05). Moreover, significant differences in BMI gain between genders were also not observed (p-value >0.05).

Figure 2: A - Means and standard errors of BMI variation between PLHIV in initial use of DTG (n=321) and in use after switching to regimens (n=293), **B** - Immunosuppressed (TCD4 < 200 cells/µL) (n= 85) and non-immunosuppressed (TCD4 ≥ 200 cells/µL) (n= 529) in a reference health center in Belo Horizonte city - MG, Brazil.



DTG: Dolutegravir; No: Individuals who started ART without DTG and who switched to DTG; Yes: Individuals who started ART with DTG; TCD4: $TCD4^{+}$ lymphocytes. Source: Authors.

Table 2: BMI variation in established times considering DTG use, immunological status, and viral load, using the Wilcoxon test.

		BMI variation (Kg/m²) Mean (SD)		
Using dolutegravir	**Time (Weeks)**	**initial use**	**use after regimen change**	***p*-value**
	24	0.53 (1.24)	0.26 (0.86)	0.021
	48	0.88 (1.76)	0.39 (1.19)	0.006
	72	0.98 (1.88)	0.43 (1.33)	0.003
	96	1.02 (1.70)	0.56 (1.48)	0.030
Immune status		**< 200 cells/µL**	**≥ 200 cells/µL**	**p-value**
	24	1.31 (1.66)	0.25 (0.88)	< 0.001
	48	1.86 (2.34)	0.41 (1.19)	< 0.001
	72	2.06 (2.38)	0.49 (1.39)	< 0.001
	96	1.76 (1.99)	0.68 (1.50)	0.002
Viral load		**< 50 copies/mL**	**≥ 50 copies/ml**	***p*-value**
	24	0.28 (0.88)	0.50 (1.22)	0.072
	48	0.37 (1.13)	0.87 (1.76)	0.008
	72	0.36 (1.28)	1.00 (1.87)	< 0.001
	96	0.43 (1.35)	1.07 (1.72)	0.005

SD: Standard deviation; DTG: Dolutegravir; TCD4+: TCD4+ lymphocytes. Source: Authors.

Multivariate analysis showed an association between BMI changes and DTG use length (p-value <0.001), ART scheme with DTG (p-value <0.05), individuals with TCD4+ <200 cells/µL (p-value <0.001), individuals in underweight BMI category (p-value <0.05), and individual age (p-value <0.05). Black skin color did not present a significant association with the final model, although it was statistically significant in the whole model over the 96 weeks compared to white individuals (p-value <0.05). Although the other variables can influence the final model, they did not show significant associations with BMI changes.

Table 3 shows the significant contribution of time and immunological status (TCD4+) on model estimation, with high statistical significance (p-value <0.0001) when compared to the respective reference factors. The Wald-test results for the complete and final models confirmed the significant differences in BMI changes over time for the variables time, initial DTG use, age, number of TCD4+ lymphocytes, and BMI category (p-value <0.05). The Wald test showed consistency of model fit (p-value <0.05; df=19). Except for the variable gender in the complete model, all the others had a VIF result greater than five, that is, there is a probability of multicollinearity between the independent variables. After fitting, all variables in the final model showed VIF very close to one, thus low probability multicollinearity.

Table 3: Results of longitudinal multivariate analyses referring to BMI changes before and after statistical model fit (estimation, standard error, and *p*-value of the model - GEE).

	Complete model			**Final model**		
	Estimation	**Standard error**	***p*-value**	**Estimation**	**Standard error**	***p*-value**
(Intercept)	0.350	0.463	0.449	0.632	0.243	< 0.001
Time [T_0]	Ref			Ref		
Time [T_{24}]	0.350	0.046	< 0.001	0.349	0.046	< 0.001
Time [T_{48}]	0.596	0.065	< 0.001	0.596	0.065	< 0.001
Time [T_{72}]	0.709	0.077	< 0.001	0.713	0.077	< 0.001
Time [T_{96}]	0.855	0.098	< 0.001	0.857	0.098	< 0.001
Initial use of DTG [No]	Ref			Ref		
Initial use of DTG [Yes]	-0.019	0.161	0.908	0.172	0.070	0.013
Sex [Male]	Ref			-	-	-
Sex [Female]	-0.167	0.118	0.157	-	-	-
Age*	0.000	0.012	0.967	0.007	0.003	0.008
Age range [21-30]	Ref			-	-	-
Age range [18-20]	0.091	0.296	0.759	-	-	-
Age range [31-40]	-0.006	0.132	0.962	-	-	-
Age range [41-50]	0.301	0.220	0.170	-	-	-
Age range [51-60]	0.179	0.336	0.595	-	-	-
Age range [61-70]	0.265	0.480	0.581	-	-	-
Age range [71-80]	-0.130	0.602	0.828	-	-	-
Age range [81-90]	-0.300	0.725	0.678	-	-	-
TCD4+ [< 200 cells/µL]	Ref			Ref		
TCD4+ [≥ 200 cells/µL]	-0.676	0.137	< 0.001	-0.747	0.139	< 0.001
Viral load [≥ 50 copies/mL]	Ref			-	-	-
Viral load [> 50 copies/mL]	0.216	0.153	0.159	-	-	-
Skin color [White]	Ref			-	-	-
Skin color [Brown]	0.048	0.078	0.543	-	-	-
Skin color [Black]	0.272	0.121	0.025	-	-	-
Skin color [Non-informed /others]	0.0367	0.142	0.796	-	-	-
Initial BMI [Eutrophic]	Ref			Ref		
Initial BMI [Underweight]	0.336	0.170	0.048	0.33401	0.17268	0.053
Initial BMI [Overweight]	-0.091	0.075	0.228	-0.05555	0.07317	0.448
Initial BMI [Obese]	-0.217	0.119	0.070	-0.21082	0.11413	0.064

Years of schooling [1 to 3 years]	Ref			-	-	-
Years of schooling [4 to 7 years]	0.201	0.238	0.398	-	-	-
Years of schooling [8 to 11 years]	-0.096	0.207	0.643	-	-	-
Years of schooling [12 or more]	-0.056	0.210	0.788	-	-	-
Years of schooling [non-informed]	-0.019	0.212	0.930	-	-	-
Blood pressure status [Hypertensive]	Ref			-	-	-
Blood pressure status [Normotensive]	-0.023	0.079	0.767	-	-	-
Marital status [With spouse]	Ref			-	-	-
Marital status [Without spouse]	0.093	0.128	0.467	-	-	-
Marital status [Non-informed]	0.146	0.161	0.365			

* Continuous variable; Ref.: Reference. Source: Authors.

4. Discussion

Either individuals who started ART with DTG or who switched to DTG containing regimens had their BMI increased. However, weight gain was significantly greater for those who started ART with DTG. These individuals may more easily develop comorbidities, such as obesity, depending on their initial BMI category. Moreover, DTG use duration, ART initiation with DTG use, immune status (TCD4+ <200 cells/ μL), and low-weight and younger individuals were associated with BMI increases.

Sociodemographic distribution was diverse, although some parameters approached the PLHIV characteristics in Brazil. According to the HIV/AIDS Epidemiological Bulletin of 2019, of the Ministry of Health of Brazil (BRASIL, 2019), HIV-infection notifications were mostly related to men (69%), brown-skinned (41.5%), and aged between 20-34 years (52.7%).

Quantitative differences among groups of individuals were expected in terms of clinical data. Two distinct groups were observed, one with individuals starting ART using DTG after HIV infection diagnosis (i.e., with the virus at detectable levels), and the other with individuals who had already started ART and then switched to regimens with DTG after viral load remission.

Regarding the BMI category, the highest percentage of underweight and eutrophic individuals (66.9%) among those who started ART with DTG is consistent with the clinical conditions presented and widely mentioned in the literature. Individuals with a high viral load and weakened immune systems tend to have lipodystrophy as they lose weight (Koethe et al., 2020). However, about 40% of the individuals had BMI classified as overweight or obese. For these, ART with DTG use may require care or monitoring of weight changes. An increase in individuals classified as overweight and obese between 49 and 96 weeks, especially among those who started ART with DTG use, corroborates the findings of Bakal et al. (2018), wherein the use of INI at the beginning of ART and higher initial BMI values are pointed out as risk factors for the development of obesity.

The results for individuals initiating ART with DTG use were similar to those from randomized clinical trials and cohorts that have already been conducted. The difference in BMI changes between males and females should be viewed with caution since women were in a smaller number (14.2%) in this study. Although this difference is not significant, our results tend to corroborate most of those found in clinical trials already performed. Venter et al. (2019) reported a significant weight increase in men (3.0 kg) and women (3.2 kg) after 48 weeks using TDF + emtricitabine (FTC) + DTG. Likewise, Sax et al. (2019) observed a mean increase of 3.24 kg in individuals using DTG associated with FTC and 3TC or tenofovir alafenamide fumarate (TAF), especially among black women.

Immunosuppression (TCD4+ <200 cells/μL) was associated with weight regain by individuals after starting ART (p-value <0.0001). In other studies such as those of Sax et al. (2019), Bakal et al. (2018), and Yuh et al. (2015), immunosuppression

was also described as an associated factor. A low baseline TCD4+ cell counts and high baseline rates of HIV RNA-HIV-1, especially in individuals initiated on ART with DTG, were correlated with weight gain in our models. These results support the contribution of the immune reconstitution process in PLHIV that are initiating ART (Bakal et al., 2018). In individuals on ART who underwent a switch to regimens using DTG, changes in BMI were attenuated, probably because their immune system had already been re-established through ART in terms of viral replication control, as well as production and maintenance of TCD4+ lymphocytes. Weight regain may be desirable, especially in underweight individuals, but it can also contribute to excessive weight gain in those at an early stage of HIV infection and in those who are eutrophic or overweight. Koethe et al. (2020) reported changes in fat levels, especially gains, as well as changes in metabolic, catabolic, and lipid storage pathways in individuals on ART, which, unlike lipodystrophy, are aggravated as the worldwide prevalence of obesity increases. HIV became a chronic disease with the use of ART, but the improvement in quality of life brought other concerns of non-communicable chronic diseases prevalent in the general population, such as diabetes, cardiovascular disease, and arterial hypertension. For this reason, anthropometric and metabolic changes have been a matter of concern in PLHIV, as they contribute to a higher risk of developing cardiovascular and metabolic diseases, and may also affect the self-esteem of this population (Castro, Silveira, Falco, Nery, & Turchi, 2016).

Although no correlation was found between age and BMI variation in the univariate analysis, the multivariate model showed a positive and significant influence (p-value <0.001). Such a result corroborates those of Koethe et al. (2016) and Debroy et al. (2019), in which the multivariate model showed an association of ages close to 35 years and over 36 years, respectively, as well as low TCD4+ cell counts, with BMI increases in individuals who started ART. This may be related to a reduction in lipid turnover, which is affected by age in the general population. Over time, adipose tissue cells tend to decrease in volume, but the occurrence of hyperplasia promotes a significant increase in the number of adipocytes (Arner et al., 2019). Other factors such as decreased testosterone and estrogens are also associated with age, leading to body fat accumulation (Oliveira, Peruch, Gonçalves, & Haas, 2016; Trabert et al., 2013).

Duration of DTG use was the main factor for changes in BMI both in individuals starting ART with DTG and in those who received DTG after changing the regimen. A significant difference was also observed between these groups when compared in the same periods. These findings are in line with those of Debroy et al. (2019); Sax et al. (2019); and Hill, Waters, & Pozniak. (2019), in which increases in body weight and hence BMI in individuals on ART were observed, with greater gains for those using INI. In a cohort of 22,972 PLHIV in the US, individuals who started ART with INI use had an average weight gain of 5.9 kg within five years, while those who used non-nucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor (PI) showed weight gains of 3.7 and 5.5 kg, respectively (Bourgi et al., 2020). Koethe et al. (2016) verified in more than 14,000 individuals that, after three years of ART, 22% of those who at the beginning of the study had a normal BMI (18.5–24.9 kg/m^2) became overweight (25.0–29.9 kg/m^2), whereas 18% of those who were overweight at the beginning of the study went into the obese category (>30 Kg/m^2).

The present study has limitations including lack of data on caloric intake, alcohol consumption, concomitant use of other medications, or fitness level for individuals. Moreover, no other anthropometric measurements were used, such as waist circumference or waist-to-hip ratio. The study also showed a low number of females, which may increase the margin of error for changes in BMI. Finally, according to the daily routine of the health service, weight measurements were recorded in clinical records at random periods, without a regular interval for consultations.

As for strengths, the study had a high number of evaluated individuals, which allowed for comparisons between therapeutic regimens, a diversification of individuals concerning years of study, skin color, and follow-up time. Furthermore, to date, this is the first study in Brazil that concomitantly evaluated changes in BMI for individuals who initiated or switched to an ART regimen with DTG use.

5. Conclusion

Antiretroviral regimens containing dolutegravir suggest weight gain with a consequent change in BMI, both in individuals starting ART with DTG use and who used DTG after changing the therapeutic regimen. Individuals who started ART with DTG use had significantly higher weight gains. Factors such as length of DTG use, starting ART with DTG use, immunological status (TCD4+ lymphocyte count <200 cells/μL), individuals with BMI <18.5 kg/m^2, and age were associated with an increase in BMI. BMI changes due to DTG use associated with female sex and skin color need more evidence to reach more representative results.

These findings show the importance of guiding the entire clinical staff regarding the care of people living with HIV in terms of potential body mass changes, especially in overweight or obese individuals who start ART with GTD use, which may develop other comorbidities, especially obesity.

Other studies involving the use of switching from ART to regimens containing dolutegravir should be carried out to assess possible changes in cholesterol and glucose levels.

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Conflict of interest

The authors declare no conflict of interest.

References

Adam, May, M. T., Vehreschild, J.-J., Obel, N., Gill, M. J., Crane, H. M., & Sterne, J. A. C. (2017). Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. *The Lancet. HIV*, *4*(8), e349–e356. https://doi.org/10.1016/S2352-3018(17)30066-8

Arner, P., Bernard, S., Appelsved, L., Fu, K. Y., Andersson, D. P., Salehpour, M., & Spalding, K. L. (2019). Adipose lipid turnover and long-term changes in body weight. *Nature Medicine*, *25*(9), 1385–1389. https://doi.org/10.1038/s41591-019-0565-5

Bakal, D. R., Coelho, L. E., Luz, P. M., Clark, J. L., De Boni, R. B., Cardoso, S. W., & Grinsztejn, B. (2018). Obesity following ART initiation is common and influenced by both traditional and HIV-/ART-specific risk factors. *Journal of Antimicrobial Chemotherapy*, *73*(8). https://doi.org/10.1093/jac/dky145

Bourgi, K., Jenkins, C. A., Rebeiro, P. F., Palella, F., Moore, R. D., Altoff, K. N., & Koethe, J. R. (2020). Weight gain among treatment-naïve persons with HIV starting integrase inhibitors compared to non-nucleoside reverse transcriptase inhibitors or protease inhibitors in a large observational cohort in the United States and Canada. *Journal of the International AIDS Society*, *23*(4), 1–8. https://doi.org/10.1002/jia2.25484

BRASIL. (2018). Protocolo clínico e diretrizes terapêuticas para o manejo da infecção pelo hiv em adultos. In *Ministério da Saúde. Secretaria de Vigilância em Saúde* (1st ed., p. 410). Retrieved from http://www.aids.gov.br/pt-br/pub/2013/protocolo-clinico-e-diretrizes-terapeuticas-para-manejo-da-infeccao-pelo-hiv-em-adultos

BRASIL. (2019). *Boletim Epidemiológico HIV / Aids | 2019*. Brasilia-DF: Ministério da Saúde. Secretaria de Vigilância em Saúde.

Castelo Filho, A., & Pott-Junior, H. (2016). Simplificação do tratamento antirretroviral combinado na prática clínica. *The Brazilian Journal of Infectious Diseases*, *2*(4), 107–111. Retrieved from http://www.bjid.org.br/en-simplificacao-do-tratamento-antirretroviral-combinado-articulo-X2177511716574472

Castro, A. D. C. O., Silveira, E. A., Falco, M. D. O., Nery, M. W., & Turchi, M. D. (2016). Overweight and abdominal obesity in adults living with HIV/AIDS. *Revista Da Associacao Medica Brasileira*, *62*(4), 353–360. https://doi.org/10.1590/1806-9282.62.04.353

Debroy, P., Sim, M., Erlandson, K. M., Falutz, J., Prado, C. M., Brown, T. T., & Lake, J. E. (2019). Progressive increases in fat mass occur in adults living with HIV on antiretroviral therapy, but patterns differ by sex and anatomic depot. *Journal of Antimicrobial Chemotherapy*, *74*(4). https://doi.org/10.1093/jac/dky551

Eckard, A. R., & McComsey, G. A. (2020). Weight gain and integrase inhibitors. *Current Opinion in Infectious Diseases*, *33*(1), 10–19. https://doi.org/10.1097/QCO.0000000000000616

Halekoh, U., Højsgaard, S., & Yan, J. (2006). The R package geepack for generalized estimating equations. *Journal of Statistical Software*, *15*(2), 1–11. https://doi.org/10.18637/jss.v015.i02

Hill, A., Waters, L., & Pozniak, A. (2019). Are new antiretroviral treatments increasing the risks of clinical obesity? *Journal of Virus Eradication*, *5*(1), 41–43. https://doi.org/PMID 30800425

Hubbard, A. E., Ahern, J., Fleischer, N. L., Laan, M. Van Der, Lippman, S. A., Jewell, N., & Satariano, W. A. (2010). To GEE or not to GEE: Comparing population average and mixed models for estimating the associations between neighborhood risk factors and health. *Epidemiology*, *21*(4), 467–474. https://doi.org/10.1097/EDE.0b013e3181caeb90

Koethe, J. R., Jenkins, C. A., Lau, B., Shepherd, B. E., Justice, A. C., Tate, J. P., & Moore, R. D. (2016). Rising Obesity Prevalence and Weight Gain among Adults Starting Antiretroviral Therapy in the United States and Canada. *AIDS Research and Human Retroviruses*, *32*(1). https://doi.org/10.1089/aid.2015.0147

Koethe, J. R., Lagathu, C., Lake, J. E., Domingo, P., Calmy, A., Falutz, J., & Capeau, J. (2020). HIV and antiretroviral therapy-related fat alterations. *Nature Reviews Disease Primers*, *6*(1). https://doi.org/10.1038/s41572-020-0181-1

Lake, J. E. (2017). The Fat of the Matter: Obesity and Visceral Adiposity in Treated HIV Infection. *Current HIV/AIDS Reports*, *14*(6). https://doi.org/10.1007/s11904-017-0368-6

Obry-Roguet, V., Brégigeon, S., Cano, C. E., Lions, C., Zaegel-Faucher, O., Laroche, H., & Poizot-Martin, I. (2018). Risk factors associated with overweight and obesity in HIV-infected people: Aging, behavioral factors but not cART in a cross-sectional study. *Medicine (United States)*, *97*(23). https://doi.org/10.1097/MD.0000000000010956

Oliveira, J., Peruch, M. H., Gonçalves, S., & Haas, P. (2016). Padrão hormonal feminino : menopausa e terapia de reposição Female hormone pattern : menopause and replacement therapy. *Revista Brasileira de Análises Clínicas*, *48*(3), 198–210. Retrieved from http://www.rbac.org.br/wp-content/uploads/2016/11/RBAC-48-3-2016-completa-corrigida-22.11.16-final.pdf

Santos Pinto Guimarães, L., Naomi Hirakata, V., & Alegre, P. (2012). Use of the Generalized estimatinG eqUation model in lonGitUdinal data analysis. *Revista HCPA*, *32*(4), 503–511. Retrieved from http://seer.ufrgs.br/hcpa503

Sax, P. E., Erlandson, K. M., Lake, J. E., McComsey, G. A., Orkin, C., Esser, S., & Koethe, J. R. (2019). Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials. *Clinical Infectious Diseases*, (Xx Xxxx), 1–11. https://doi.org/10.1093/cid/ciz999

Trabert, B., Graubard, B. I., Nyante, S. J., Rifai, N., Bradwin, G., Elizabeth, A., & Mcglynn, K. A. (2013). Relationship of sex steroid hormones with body size and with body composition measured by dual-energy X-ray absorptiometry in US men. *Cancer Causes Control*, *23*(12), 1881–1891. https://doi.org/10.1007/s10552-012-0024-9.Relationship

Venter, W. D. F., Moorhouse, M., Sokhela, S., Fairlie, L., Mashabane, N., Masenya, M., & Hill, A. (2019). Dolutegravir plus two different prodrugs of tenofovir to treat HIV. *New England Journal of Medicine*, *381*(9), 803–815. https://doi.org/10.1056/NEJMoa1902824

WHO. (2004). BMI Classification. https://web.archive.org/web/20090418181049/http://www.who.int/bmi/index.jsp?introPage=intro_3.html

Yuh, B., Tate, J., Butt, A. A., Crothers, K., Freiberg, M., Leaf, D., & Justice, A. C. (2015). Weight change after antiretroviral therapy and mortality. *Clinical Infectious Diseases*, *60*(12), 1852–1859. https://doi.org/10.1093/cid/civ192