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ARTIGO
ARTICLE

Which antiretroviral regimen is associated with higher adherence in Brazil? A comparison of single, multi, and dolutegravir-based regimens

Qual esquema antirretroviral está associado à maior adesão no Brasil? Uma comparação dos esquemas de comprimido único, múltiplos comprimidos e com dolutegravir

¿Qué tratamiento antirretroviral está asociado con adherencia más alta en Brasil? Una comparación de tratamientos únicos, múltiples y basados en el dolutegravir

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Abstract

We evaluated adherence to highly active antiretroviral therapy (HAART) and its associated factors according to the type of regimen in patients initiating treatment in Belo Horizonte, Minas Gerais State, Brazil. We measured adherence using the eight items Morisky Therapeutic Adhesion Scale *(MMAS-8) and compared the use of "backbone" tenofovir/lamivudine plus efavirenz one tablet once-daily (STR) or dolutegravir in multi-tablet once-daily (MTR-DTG), or other multi-tablet regimens (MTR-other). We conducted a multivariate logistic regression analysis to address factors associated with adherence. A total of 393 patients were included, 254 used STR, 106 MTR-DTG, and 33 MTR-other. The overall adhesion rate was 44.8% (95%CI: 39.4; 50.1), 50% for MTR-DTG, 43.3% for STR and 39.4% for MTR-other. Multivariate analysis showed a higher chance of adherence among patients using MTR-DTG, those who received and understood counseling about their treatment and with a higher quality of life. Prior use of illicit drugs in the lifetime was associated with poorer adherence. Overall adherence was low, highlighting the need for strategies focusing on counseling about medicines and substance use. Pill burden was not an issue for patients using MTR-DTG once-daily, who achieved better results.*

HIV; Anti-retroviral Agents; Medication Adherence; Self Report

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Introduction

The therapeutic success of highly active antiretroviral therapy (HAART) is assessed by viral suppression and its achievement requires high levels of HAART adherence, generally 95% [1,2]. Lower levels of adherence may lead to therapeutic failure, viral mutations selection and the development of resistance to medicines [3,4].

Adherence is a worldwide challenge and is associated with several factors related to the individual, to the medicines and to the health services. Major difficulties with HAART occur at the beginning of the treatment when the main factors affecting adherence are adverse reactions, number of tablets administered, level of schooling, the presence of AIDS symptoms, among others directly influencing the individual's routine [5,6].

Simplification of HAART is a worldwide trend as a strategy to increase the adherence and include the use of single tablet regimens (STR) consisting of two or more drugs in a single tablet, the use of single daily regimens, and the use of medicines with lower toxicity [7].

Previous studies have reported greater adherence to HAART for patients using STR containing tenofovir (TDF), emtricitabine (FTC) and efavirenz (EFV) [3,7,8]. In Brazil, the generic STR is available to the population since 2015, however, it contains a different formulation: TDF, lamivudine (3TC) and EFV [4]. In 2017, dolutegravir (DTG) was included in the first-line regimen for individuals initiating HAART, replacing EFV [4]. This regimen includes one tablet containing TDF/3TC plus one DTG tablet, administered once-daily. However, the impact of different administration regimens in the adherence to HAART is still unknown.

The scarcity of observational studies in HAART-naïve individuals specifically evaluating the STR containing TDF/3TC/EFV or the TDF/3TC + DTG regimen, associated to the updating of the Brazilian guidelines, highlights the need to evaluate the adherence to the regimens available to the population.

Brazil has been recognized for its strong response to the HIV epidemic. The Federal government has provided since the early 1990s generic versions of antiretroviral drugs, and, it started providing in 2013 public antiretroviral treatment to all HIV-adults seeking care, regardless of the stage of HIV they were facing. Despite of the struggle for sustainable financing of the Brazilian Unified National Health System (SUS), Brazil's national HIV and AIDS response is integrated into the country's Health Strategic Plan. The approach to HIV prevention involves promoting and improving access to HIV testing, immediate treatment for those testing positive regardless of CD4 count, and the provision of pre- and post-exposure prophylaxis [4].

Primary care in SUS expanded its services to 64% of the national population in addition to the other HIV/AIDS public services, 655 reference services, 25 laboratories for HIV-1 diagnostic, 12 services to lipodystrophy treatment, and, 101 Centers for Testing and Counseling [4].

Accordingly, we aimed to evaluate the adherence to first-line antiretroviral regimens and associated factors among individuals initiating treatment in Southeast Brazil to contribute in developing target strategies to improve patient's outcomes.

Methods

This is a baseline cross-sectional analysis of the ECOART cohort study conducted in Belo Horizonte, capital of Minas Gerais State, Brazil. We evaluated people living with HIV with at least seven and maximum 180 days of HAART usage, selected by non-randomized sampling and identified through their register on the Medication Logistics Control System (SICLOM).

Patients were recruited from September 2015 to August 2017 in three public reference services in outpatient HIV care covering about 80% of people living with HIV in the city, according to registers from the SICLOM. Service I belongs to a large hospital of the public network of Minas Gerais that provides specialized assistance with interdisciplinary care and dispensing of medication to the patient. Service II is a specialized municipal outpatient assistance and also a testing and counseling center that provides comprehensive and interdisciplinary treatment and dispensing of medicines.

Service III is also a municipal reference, and provides interdisciplinary assistance, integral and dispensing of medicines.

Inclusion criteria were individuals aged 13+ years old, attending one of the three reference services during the recruitment period, who had a minimum autonomy to answer the interview, agreed to participate in the study and signed the consent form. We obtained data through face-to-face interviews with eligible patients and complemented with national data from the Laboratory Test Control System (SISCEL) and SICLOM electronic systems from the Brazilian Ministry of Health.

The research was conducted in accordance with the *Resolution n. 466/2012* of the Brazilian National Health Council. All data collected were kept confidential and the identification of individuals was preserved. For the accomplishment of the research, we obtained the approval of the Ethics Research Committee of Minas Gerais Federal University (UFMG; CAAE-31192914.3.0000.5149) and of the participating centers.

Events and explanatory variables

Adherence (the dependent variable) was measured by self-report using the eight items *Morisky Therapeutic Adhesion Scale* (MMAS-8) [9,10,11] validated in Brazil [12]. Scores ranged from 0 to 8 points and patients who obtained 8 points (100%) were considered adherents. Independent variables were: (i) sociodemographic: sex, age, schooling level, own income, employment status, economic class, marital status; (ii) behavioral and habits of life: alcohol use, cigarette smoking, illicit drugs use in lifetime, condoms usage in the last month, risk/exposure category; (iii) clinical: AIDS-defining illness, signs and symptoms of anxiety and depression, self-reported comorbidities or coinfections; (iv) HAART-related: type of regimen, adverse reactions, number of adverse reactions, self-perception about the difficulty of treatment, time on HAART; (v) laboratory tests: CD4+ T lymphocyte count (LT-CD4+) and viral load at the beginning of HAART usage; (vi) service-related: health care unit and counseling of health professionals about HAART and (vii) quality of life.

The economy class classification was evaluated according to the Brazilian Association of Research Companies (ABEP) [13]. Data for concurrent AIDS-defining illness was obtained from patient's clinical chart and classified according to the Centers for Disease Control and Prevention definition [14]. Signs and symptoms of anxiety and depression were evaluated by the *Hospital Anxiety and Depression Scale* [15,16], with scores ranging from 0 to 14, and a cut off of ≥ 8 points for both anxiety and depression.

The HAART regimen was classified as STR (TDF/3TC/EFV one tablet once-daily), MTR-DTG once-daily (TDF/3TC + DTG once-daily) or other multiple tablet regimens (MTR-other), corresponding to all other multi-tablet multi-dose HAART regimens.

Self-perception about difficulty with treatment was measured by the following question: "Based on your experience with antiretroviral drugs so far, how would you rate your treatment on a daily basis?". Valid options of response were dichotomized as "difficult" (very difficult, difficult, medium) or "easy" (easy, very easy).

LT-CD4+ and viral load at the beginning of the treatment were retrieved from SISCEL with a tolerance of three months. Quality of life was assessed by the WHOQOL-HIV BREF instrument, with scores ranging from 0 to 20 for each one of the six domains [17,18].

The interviews were typed into Epi Info 3.5.4 software (https://www.cdc.gov/epiinfo/index.html) and 10% of the sample was retyped for quality control, achieving a perfect inter-examiner agreement (kappa statistic = 0.95) [19].

Statistical analysis

For analytic purposes, patients were compared according to the HAART regimen in use at the time of the interview: STR, MTR-DTG or MTR-other. A descriptive analysis was carried out followed by a bivariate analysis, stratified by type of regimen. The individual association of each categorical variable with adhesion was assessed by Pearson's chi-square test or Fischer's exact test, when appropriate. For continuous variables, the t-test was used.

Multivariate analysis was performed through a logistic regression model and values were presented by odds ratio (OR) with their respective 95% confidence intervals (95%CI). Variables with a p-value ≤ 0.20 in the bivariate analysis were selected to enter the initial multivariate model. The backward stepwise method was conducted until the final model contained only relevant variables (p ≤ 0,05 or with theoretical relevance). The suitability of the model was assessed by the Hosmer-Lemeshow test and by the area under the Receiver Operating Characteristics (ROC) curve, with p-values > 0.05 indicating a good fit of the model in the first test and values > 0.7 in the second one.

Statistical analyses were performed using the SPSS v. 24 (https://www.ibm.com/) at a significance level of 5% and forest plots were developed using the R (http://www.r-project.org).

Results

Among 460 eligible patients identified, 427 agreed to participate in the ECOART study. Of 427 persons, 31 were excluded due to lack of data on adherence and 3 because they had less than seven days of treatment initiation totalizing 393 (85%) in the current analysis. There were no statistically significant differences between participants and non-participants regarding sex, age or race.

Most of the participants were male (82.4%) and the main risk/exposure category corresponded to men who have sex with men – MSM (52.1%). The majority was single, divorced or widowed (79.6%) and was working at the time of the interview (61.3%). Approximately half were under 33 years old (51.1%), belonged to the economic class C (47.1%) and 38.4% had 10 to 12 years of schooling. A high proportion of patients consumed alcohol (79.6%) and used illicit drugs in the lifetime (49.7%). AIDS-defining illness occurred on 20% of participants and comorbidities were reported by 19.8% and 21.4% had signs and symptoms of depression and 31.3% of anxiety (Table 1).

Most patients used a therapeutic regimen containing 2 NRTIs + 1 NNRTI (66.7%), being TDF, 3TC, EFV the most common. STR was used by 254 (64.6%) patients, 106 (27%) used MTR-DTG regimen and 33 (8.4%) used MTR-other. Approximately 70.3% considered the treatment easy and 54.7% were on HAART for more than 60 days at the time of the interview. Of the total number of patients, 85.9% had at least one and 72.6% up to five adverse reactions.

Initial LT-CD4+ count ≤ 200cells/mm^3 was observed for 27% of patients and 26.5% started HAART with viral load greater than 100,000 copies/mL. Most patients (41.7%) attended service II and approximately 12% did not receive or did not understand the health professional counseling about HAART. Mean quality of life was higher than 14.0 in all domains, with the lowest value observed in the environment domain (14.32; SD = 2.40) and the highest in the physical domain (15.44; SD = 3.09) (Table 1).

Adherence assessment

Table 2 shows patient's responses to individual questions of the MMAS-8, where 97.7% of the patients did not take their HAART medicines because they felt better and thought the disease was under control (item 6). There was a higher frequency of responses indicating adherence among the MTR-DTG group (five items) and a lower frequency in the MTR-other group (only one item). The overall prevalence of adherence was 44.8% (n = 176) and MTR-DTG group presented the highest percentage of adherent individuals (50%), followed by the STR group (43.3%) and the MTR-other group (39.4%). However, there was no statistically significant difference between adherence to HAART among the groups and the three participanting services (p = 0.81).

The adherence to HAART in the overall population ranged from 28.6% to 61.8% according to their characteristics. Lower point estimates were observed for patients with signs and symptoms of depression (28.6%), patients who did not receive or understand health professional counseling about HAART (31.3%), patients who perceived their treatment as difficult (31.9%), patients reporting more than five adverse reactions (32.7%), those using 2 NRTI + 2 PI (33.3%) and who had used illicit drugs in the lifetime (37.4%). Higher adherence estimates were observed for individuals who did not have any adverse reaction (61.8%), were married or in a stable union (52.5%), who did not use illicit drugs in the lifetime (52.3%), aged 33 years or more (51%) and with 13+ years of schooling (47.6%) (Table 3).

Table 1

Characteristics of individuals living with HIV, according to the antiretroviral regimen used. Belo Horizonte, Minas Gerais State, Brazil, 2017 (n = 393).

Characteristics	Global (n = 393)	STR (n = 254)	MTR-DTG (n = 106)	MTR-other (n = 33)	p-value
Sociodemographic					
Sex (male)	323 (82.4)	209 (82.3)	90 (85.7)	24 (72.7)	0.23
Age (> 33 years)	192 (48.9)	117 (46.1)	50 (47.2)	25 (75.8)	0.01 *
Schooling level (years)					0.09 *
≤ 9	95 (24.2)	61 (24.0)	19 (17.9)	15 (45.5)	
10-12	151 (38.4)	104 (40.9)	37 (34.9)	10 (30.3)	
13+	147 (37.4)	89 (35.0)	50 (47.2)	8 (24.2)	
Own income in the last 6 months (yes)	324 (82.7)	211 (83.4)	88 (83.0)	25 (75.8)	0.55
Employment status (working)	241 (61.3)	165 (65.0)	62 (58.5)	14 (42.4)	0.03 *
Economic class					0.02 *
A-B	140 (36.5)	95 (38.5)	38 (35.8)	7 (22.6)	
C	181 (47.1)	109 (44.1)	58 (54.7)	14 (45.2)	
D-E	63 (16.4)	43 (17.4)	10 (9.4)	10 (32.3)	
Marital status (married/stable union)	80 (20.4)	51 (20.1)	17 (16.0)	12 (36.4)	0.04 *
Behavioral and habits of life					
Ever used alcohol (yes)	313 (79.6)	207 (81.5)	82 (77.4)	24 (72.7)	0.40
Currently smoker (yes)	102 (26.0)	66 (26.0)	29 (27.4)	7 (21.2)	0.78
Ever used any illicit drug (yes)	195 (49.7)	123 (48.4)	60 (56.6)	12 (37.5)	0.13
Condom use in all sexual intercourses in the last month (yes)	222 (70.3)	141 (67.1)	64 (76.2)	17 (77.3)	0.23
Risk/Exposure category (MSM)	198 (52.1)	134 (54.3)	52 (51.5)	12 (37.5)	0.20
Clinical					
AIDS defining illness (AIDS)	76 (20.0)	57 (23.1)	6 (5.9)	13 (40.6)	< 0.01 *
Anxiety (yes)	123 (31.3)	81 (31.9)	28 (26.4)	14 (42.4)	0.21
Depression (yes)	84 (21.4)	59 (23.2)	15 (14.2)	10 (33.3)	0.07
Comorbidities (yes)	78 (19.8)	51 (20.1)	13 (12.3)	14 (42.4)	< 0.01 *
Coinfections (yes)	28 (7.2)	22 (8.7)	2 (1.9)	4 (12.1)	0.04 *
HAART-related					
Classical therapeutic regimen					-
2 NRTI + 1 NNRTI	262 (66.7)	254 (100.0)	-	8 (24.2)	
2 NRTI + 1 IIN	110 (28.0)	-	106 (100.0)	4 (12.1)	
2 NRTI + 2 PI	21 (5.3)	-	-	21 (63.6)	
Adverse reactions (yes)	335 (85.9)	226 (89.7)	81 (76.4)	28 (87.5)	< 0.01 *
Number of adverse reactions (> 5)	107 (27.4)	85 (33.7)	10 (9.4)	12 (37.5)	< 0.01 *
Self-perception of treatment difficulty (easy)	275 (70.3)	173 (68.7)	87 (82.1)	15 (45.5)	< 0.01 *
Time since treatment initiation (> 60 days)	214 (54.7)	152 (60.1)	38 (35.8)	24 (75.0)	< 0.01 *
Laboratory tests (before HAART)					
CD4+ T lymphocyte count (≤ 200cells/mm^3)	88 (27.0)	63 (30.0)	14 (15.6)	11 (42.3)	0.01 *
Viral load (> 100,000 copies/mL)	87 (26.5)	60 (28.2)	15 (17.2)	12 (42.9)	0.02 *
Health service-related					
Healthcare facility					< 0.01 *
I	145 (36.9)	125 (49.2)	0 (0.0)	20 (60.6)	
II	164 (41.7)	106 (41.7)	47 (44.3)	11 (33.3)	
III	84 (21.4)	23 (9.1)	59 (55.7)	2 (6.1)	
Receiving and understanding HAART counseling (Yes)	343 (87.7)	222 (88.1)	93 (87.7)	28 (84.8)	0.87
WHOQOL-HIV BREF domains [Mean (SD)]					
Physical	15.44 (3.09)	15.32 (3.04)	16.12 (2.63)	14.18 (4.18)	< 0.01 *
Psychological	14.98 (2.83)	14.94 (2.92)	15.43 (2.27)	13.82 (3.46)	0.02 *
Independence	15.43 (2.75)	15.47 (2.78)	15.66 (2.37)	14.39 (3.36)	0.07 *
Social	15.20 (3.01)	15.07 (3.11)	15.72 (2.54)	14.48 (3.53)	0.08
Environment	14.32 (2.40)	14.31 (2.45)	14.51 (2.22)	13.86 (2.50)	0.40
Spiritual	14.66 (3.65)	14.34 (3.70)	15.43 (3.27)	14.69 (4.18)	0.04 *

HAART: highly active antiretroviral therapy; IIN: integrase inhibitor; MSM: men who have sex with men; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; MTR-DTG: multi-tablet regimen once daily with dolutegravir – TDF/3TC + DTG; MTR-other: multi-tablet multi-dose; SD: standard deviation; STR: single tablet regimen – TDF/3TC/EFV.

* Statistical difference.

Table 2

Individual answers to the eight items *Morisky Therapeutic Adhesion Scale* (MMAS-8) and summary scores, according to the antiretroviral regimen used. Belo Horizonte, Minas Gerais State, Brazil, 2017 (n = 393).

MMAS-8 items *	Global (n = 393) n (%)	STR (n = 254) n (%)	MTR-DTG (n = 106) n (%)	MTR-other (n = 33) n (%)
1. Do you sometimes forget to take your medicine? (no)	311 (79.1)	202 (79.5)	84 (79.2)	25 (75.8)
2. Thinking over the past 2 weeks, were there any days when you did not take your medicine? (no)	328 (83.5)	209 (82.3)	95 (89.6)	24 (72.7)
3. Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it? (no)	375 (95.4)	240 (94.5)	106 (100.0)	29 (87.9)
4. When you travel or leave home, do you sometimes forget to bring along your medicine? (no)	361 (91.9)	229 (90.2)	100 (94.3)	32 (97.0)
5. Did you take all your medicines yesterday? (yes)	355 (90.3)	225 (88.6)	103 (97.2)	27 (81.8)
6. When you feel like your symptoms are under control, do you sometimes stop taking your medicine? (no)	384 (97.7)	247 (97.2)	106 (100.0)	31 (93.9)
7. Do you ever feel hassled about sticking to your treatment plan? (no)	317 (80.7)	202 (79.5)	92 (86.8)	23 (69.7)
8. How often do you have difficulty remembering to take all your medicine? (never)	258 (65.6)	170 (66.9)	64 (60.4)	24 (72.7)
Adherence prevalence [95%CI]	176 (44.8) [39.4; 50.1]	110 (43.3) [36.9; 49.4]	53 (50.0) [40.4; 59.6]	13 (39.4) [22.2; 57.9]

95%CI: 95% confidence interval; MTR-DTG: multi-tablet regimen once daily with dolutegravir – TDF/3TC + DTG; MTR-other: multi-tablet multi-dose; STR: single tablet regimen – TDF/3TC/EFV.

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Additionally, the estimates of the prevalence of adherence to HAART according to the characteristics of the populations within the STR, MTR-DTG and MTR-other subgroups followed the same trend of the overall population, with few exceptions (Table 3).

Multivariate analysis

Figure 1 shows the results of the multivariate modeling conducted to compare the chance of adherence according to the potential explanatory factors. For the overall sample, the use of HAART regimens containing MTR-DTG ($p = 0.01$), receiving and understanding counseling about HAART ($p = 0.03$) and the physical and social domains of quality of life ($p < 0.04$) were associated with higher chance of HAART adherence, while the use of illicit drugs at the lifetime ($p < 0.01$) was associated with a lower chance. In addition, the presence of AIDS-defining symptoms showed a trend to be associated with higher adherence ($p = 0.05$) (Figure 1a).

Multivariate analysis restricted to the STR subgroup showed self-perception of treatment as easy ($p = 0.04$), receiving and understanding counseling about HAART ($p = 0.04$), and the social domain of quality of life ($p = 0.04$) were associated with higher chance of adherence, while having used illicit drugs at lifetime ($p = 0.01$) and occurrence of adverse reactions ($p = 0.07$) were associated with lower chance, although the adverse reactions results were not statistically significant (Figure 1b). For the MTR-DTG and MTR-other subgroups, quality of life domains were associated with higher chance of HAART adherence: the physical domain ($p = 0.01$) for individuals in the MTR-DTG group and the psychological domain ($p = 0.03$) for individuals in the MTR-other group (Figure 1c and 1d). In addition, being employed (0.07) and the presence of AIDS-defining symptoms ($p = 0.09$) showed a trend to be associated with a higher adherence chance among the MTR-DTG group (Figure 1c).

Table 3

Prevalence of adherence to highly active antiretroviral therapy (HAART), according to the antiretroviral regimen used and other characteristics of individuals living with HIV. Belo Horizonte, Minas Gerais State, Brazil, 2017 (n = 393).

Characteristics	Global (n = 393)		STR (n = 254)		MTR-DTG (n = 106)		MTR-other (n = 33)	
	n (%)	95%CI	n (%)	95%CI	n (%)	95%CI	n (%)	95%CI
Sociodemographic								
Sex								
Male	145 (44.9)	39.4; 50.5	93 (44.5)	37.6; 51.5	43 (47.8)	37.1; 58.6	9 (37.5)	18.8; 59.4
Female	30 (43.5)	31.6; 56.0	17 (37.8)	23.8; 53.5	9 (60.0)	32.3; 83.7	4 (44.4)	13.7; 78.8
Age (years)								
≤ 33	78 (38.8)	32.0; 45.9	52 (38.0)	29.8; 46.6	25 (44.6)	31.3; 58.5	1 (12.5)	0.3; 52.7
> 33	98 (51.0)	43.7; 58.3	58 (49.6)	40.2; 59.0	28 (56.0)	41.3; 70.0	12 (48.0)	27.8; 68.7
Schooling level (years)								
≤ 9	40 (42.1)	32.0; 52.7	24 (39.3)	27.1; 52.7	9 (47.4)	24.4; 71.1	7 (46.7)	21.3; 73.4
10-12	66 (43.7)	35.7; 52.0	45 (43.3)	33.6; 53.3	19 (51.4)	34.4; 68.1	2 (20.0)	2.5; 55.6
13+	70 (47.6)	39.3; 56.0	41 (46.1)	35.4; 57.0	25 (50.0)	35.5; 64.5	4 (50.0)	15.7; 84.3
Own income in the last 6 months								
Yes	146 (45.1)	39.6; 50.7	92 (43.6)	36.8; 50.6	44 (50.0)	39.1; 60.9	10 (40.0)	21.1; 61.3
No	29 (42.6)	30.7; 55.2	17 (40.5)	25.6; 56.7	9 (50.0)	26.0; 74.0	3 (37.5)	8.5; 75.5
Employment status								
Working	115 (47.7)	41.3; 54.2	72 (43.6)	35.9; 51.6	36 (58.1)	44.8; 70.5	7 (50.0)	23.0; 77.0
Not working	61 (40.1)	32.3; 48.4	38 (42.7)	32.3; 53.6	17 (38.6)	24.4; 54.5	6 (31.6)	12.6; 56.6
Economic class								
A-B	64 (45.7)	37.3; 54.3	42 (44.2)	34.0; 54.8	20 (52.6)	35.8; 69.0	2 (28.6)	3.7; 71.0
C	88 (48.6)	41.1; 56.1	51 (46.8)	37.2; 56.6	29 (50.0)	36.6; 63.4	8 (57.1)	28.9; 82.3
D-E	21 (33.3)	22.0; 46.3	14 (32.6)	19.1; 48.5	4 (40.0)	12.2; 73.8	3 (30.0)	6.7; 65.2
Marital status								
Single/Divorced/ Widowed	134 (42.8)	37.3; 48.5	84 (41.4)	34.5; 48.5	41 (46.1)	35.4; 57.0	9 (42.9)	21.8; 66.0
Married/Stable union	42 (52.5)	41.0; 63.8	26 (51.0)	36.6; 65.2	12 (70.6)	44.0; 89.7	4 (33.3)	9.9; 65.1
Behavioral and habits of life								
Alcohol use								
Yes	137 (43.8)	38.2; 49.5	89 (43.0)	36.2; 50.0	40 (48.8)	37.6; 60.1	8 (33.3)	15.6; 55.3
No	39 (48.8)	37.4; 60.2	21 (44.7)	30.2; 59.9	13 (54.2)	32.8; 74.4	5 (55.6)	21.2; 86.3
Currently smoker								
Yes	42 (41.2)	31.5; 51.4	25 (37.9)	26.2; 50.7	15 (51.7)	32.5; 70.6	2 (28.6)	3.7; 71.0
No	134 (46.0)	40.2; 52.0	85 (45.2)	38.0; 52.6	38 (49.4)	37.8; 61.0	11 (42.3)	23.4; 63.1
Ever used any illicit drug								
Yes	73 (37.4)	30.6; 44.6	42 (34.1)	25.8; 43.2	27 (45.0)	32.1; 58.4	4 (33.3)	9.9; 65.1
No	103 (52.3)	45.1; 59.4	68 (51.9)	43.0; 60.7	26 (56.5)	41.1; 71.1	9 (45.0)	23.1; 68.5
Condom use								
Yes	95 (42.8)	36.2; 49.6	56 (39.7)	31.6; 48.3	32 (50.0)	37.2; 62.8	7 (41.2)	18.4; 67.1
No	43 (45.7)	35.4; 56.3	31 (44.9)	32.9; 57.4	11 (55.0)	31.5; 76.9	1 (20.0)	0.5; 71.6
Risk/Exposure category								
MSM	90 (45.5)	38.4; 52.7	59 (44.0)	35.5; 52.9	25 (48.1)	34.0; 62.4	6 (50.0)	21.1; 78.9
Other	81 (44.5)	37.2; 52.0	47 (41.6)	32.4; 51.2	27 (55.1)	40.2; 69.3	7 (35.0)	15.4; 59.2

(continues)

Table 3 (continued)

Characteristics	Global (n = 393)		STR (n = 254)		MTR-DTG (n = 106)		MTR-other (n = 33)	
	n (%)	95%CI	n (%)	95%CI	n (%)	95%CI	n (%)	95%CI
Clinical								
AIDS defining illness								
Non-AIDS	131 (43.1)	37.5; 48.9	78 (41.1)	34.0; 48.4	47 (49.5)	39.1; 59.9	6 (31.6)	12.6; 56.6
AIDS	40 (52.6)	40.8; 64.2	28 (49.1)	35.6; 62.7	5 (83.3)	35.9; 99.6	7 (53.8)	25.1; 80.8
Anxiety								
Yes	48 (39.0)	30.4; 48.2	31 (38.3)	27.7; 49.7	14 (50.0)	30.6; 69.4	3 (21.4)	4.7; 50.8
No	128 (47.4)	41.3; 53.5	79 (45.7)	38.1; 53.4	39 (50.0)	38.5; 61.5	10 (52.6)	28.9; 75.6
Depression								
Yes	24 (28.6)	19.2; 39.5	17 (28.8)	17.8; 42.1	5 (33.3)	11.8; 61.6	2 (20.0)	2.5; 55.6
No	152 (49.2)	43.5; 54.9	93 (47.7)	40.5; 54.9	48 (52.7)	42.0; 63.3	11 (47.8)	26.8; 69.4
Comorbidities								
Yes	35 (44.9)	33.6; 56.6	24 (47.1)	32.9; 61.5	8 (61.5)	31.6; 86.1	3 (21.4)	4.7; 50.8
No	141 (44.8)	39.2; 50.4	86 (42.4)	35.5; 49.5	45 (48.4)	37.9; 59.0	10 (52.6)	28.9; 75.6
Coinfections								
Yes	13 (46.4)	27.5; 66.1	11 (50.0)	28.2; 71.8	2 (100.0)	100.0; 100.0	0 (0.0)	0.0; 60.2
No	162 (44.6)	39.5; 49.9	98 (42.6)	36.1; 49.3	51 (49.0)	39.1; 59.0	13 (44.8)	26.4; 64.3
HAART-related								
Classical therapeutic regimen								
2 NRTI + 1 NNRTI	115 (43.9)	37.8; 50.1	110 (43.3)	37.1; 49.6	*	*	5 (62.5)	24.5; 91.5
2 NRTI + 1 IIN	54 (49.1)	39.4; 58.8	-	-	53 (50.0)	40.1; 59.9	1 (25.0)	0.6; 80.6
2 NRTI + 2 PI	7 (33.3)	14.6; 57.0	-	-	*	*	7 (33.3)	14.6; 57.0
Adverse reactions								
Yes	141 (42.1)	36.8; 47.6	92 (40.7)	34.2; 47.4	40 (49.4)	38.1; 60.7	9 (32.1)	15.9; 52.4
No	34 (61.8)	47.7; 74.6	17 (65.4)	44.3; 82.8	13 (52.0)	31.3; 72.2	4 (100.0)	100.0; 100.0
Number of adverse reactions								
≤ 5	140 (49.5)	43.5; 55.5	81 (48.5)	40.7; 56.3	49 (51.0)	40.6; 61.4	10 (50.0)	27.2; 72.8
> 5	35 (32.7)	24.0; 42.5	28 (32.9)	23.1; 44.0	4 (40.0)	12.2; 73.8	3 (25.0)	5.5; 57.2
Self-perception of treatment difficulty								
Easy	139 (50.5)	44.5; 56.6	87 (50.3)	42.6; 58.0	44 (50.6)	39.6; 61.5	8 (53.3)	26.6; 78.7
Difíccult	37 (31.9)	23.6; 41.2	23 (29.1)	19.4; 40.4	9 (47.4)	24.4; 71.1	5 (27.8)	9.7; 53.5
Time on HAART (days)								
≤ 60	87 (49.2)	41.6; 56.8	46 (45.5)	35.6; 55.8	37 (54.4)	41.9; 66.5	4 (50.0)	15.7; 84.3
> 60	89 (41.6)	34.9; 48.5	64 (42.1)	34.2; 50.4	16 (42.1)	26.3; 59.2	9 (37.5)	18.8; 59.4
Laboratorial (before HAART)								
CD4+ T lymphocyte count (cells/mm3)								
≤ 200	44 (50.0)	39.1; 60.9	34 (54.0)	40.9; 66.6	7 (50.0)	23.0; 77.0	3 (27.3)	6.0; 61.0
> 200	99 (41.6)	35.3; 48.1	58 (39.5)	31.5; 47.8	36 (47.4)	35.8; 59.2	5 (33.3)	11.8; 61.6
Viral load (copies/mL)								
≤ 100,000	105 (43.6)	37.2; 50.1	67 (43.8)	35.8; 52.0	33 (45.8)	34.0; 58.0	5 (31.3)	11.0; 58.7
> 100,000	40 (46.0)	35.2; 57.0	27 (45.0)	32.1; 58.4	8 (53.3)	26.6; 78.7	5 (41.7)	15.2; 72.3

(continues)

Table 3 (continued)

Characteristics	Global (n = 393)		STR (n = 254)		MTR-DTG (n = 106)		MTR-other (n = 33)	
	n (%)	95%CI	n (%)	95%CI	n (%)	95%CI	n (%)	95%CI
Health service-related								
Healthcare facility								
I	68 (46.9)	38.6; 55.4	59 (47.2)	38.2; 56.3	0 (0.0)	*	9 (45.0)	23.1; 68.5
II	71 (43.3)	35.6; 51.2	43 (40.6)	31.1; 50.5	25 (53.2)	38.1; 67.9	3 (27.3)	6.0; 61.0
III	37 (44.0)	33.2; 55.3	8 (34.8)	16.4; 57.3	28 (47.5)	34.3; 60.9	1 (50.0)	1.3; 98.7
Receiving and understanding HAART counseling								
Yes	160 (46.6)	41.3; 52.1	103 (46.4)	39.7; 53.2	45 (48.4)	37.9; 59.0	12(42.9)	24.5; 62.8
No	15 (31.3)	18.7; 46.3	6 (20.0)	7.7; 38.6	8 (61.5)	31.6; 86.1	1 (20.0)	0.5; 71.6

95%CI: 95% confidence interval; HAART: highly active antiretroviral therapy; IIN: integrase inhibitor; MSM: men who have sex with men; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; MTR-DTG: multi-tablet regimen once daily with dolutegravir – TDF/3TC + DTG; MTR-other: multi-tablet multi-dose; STR: single tablet regimen – TDF/3TC/EFV.
* Not estimable.

All models presented a good fit, with Hosmer-Lemeshow test and the ROC curve values lower than 0.05 and higher than 0.7, respectively. Specific values were p = 0.17 and ROC = 0.7 for the global model, p = 0.55 and ROC = 0.7 for STR model, p = 0.48 and ROC = 0.7 for MTR-DTG model and p = 0.41 and ROC = 0.8 for the MTR-other model.

Discussion

In this cross-sectional study, which included individuals at the beginning of treatment, the overall rate of adherence was 44.8%, measured by the MMAS-8 self-report scale. Despite having no differences between the HAART subgroups in the raw analysis, multivariate modeling showed a higher chance of adherence among patients using the multi-table once-daily regimen containing TDF/3TC + DTG. In addition, different factors influenced the adherence in each subgroup.

Regarding the characteristics of the sample, there was a predominance of males, MSM, aged less than 33 years, with 10 to 12 years of schooling, with their own income in the last six months, employed and single, divorced or widowed. These results are consistent with the profile of the Brazilian people living with HIV and the trend of increase of the HIV epidemic among young MSM [6,20].

The overall prevalence of adherence observed in the present study was similar to the ones reported in Brazil in earlier years [21,22] and worldwide [23,24,25]. Previous studies using the MMAS-8 with the same cut-off point as ours reported a prevalence of adherence of 43.7% [24] and 61.7% [25], while studies using other self-report measurements of adherence reported rates above 70% [3,26,27].

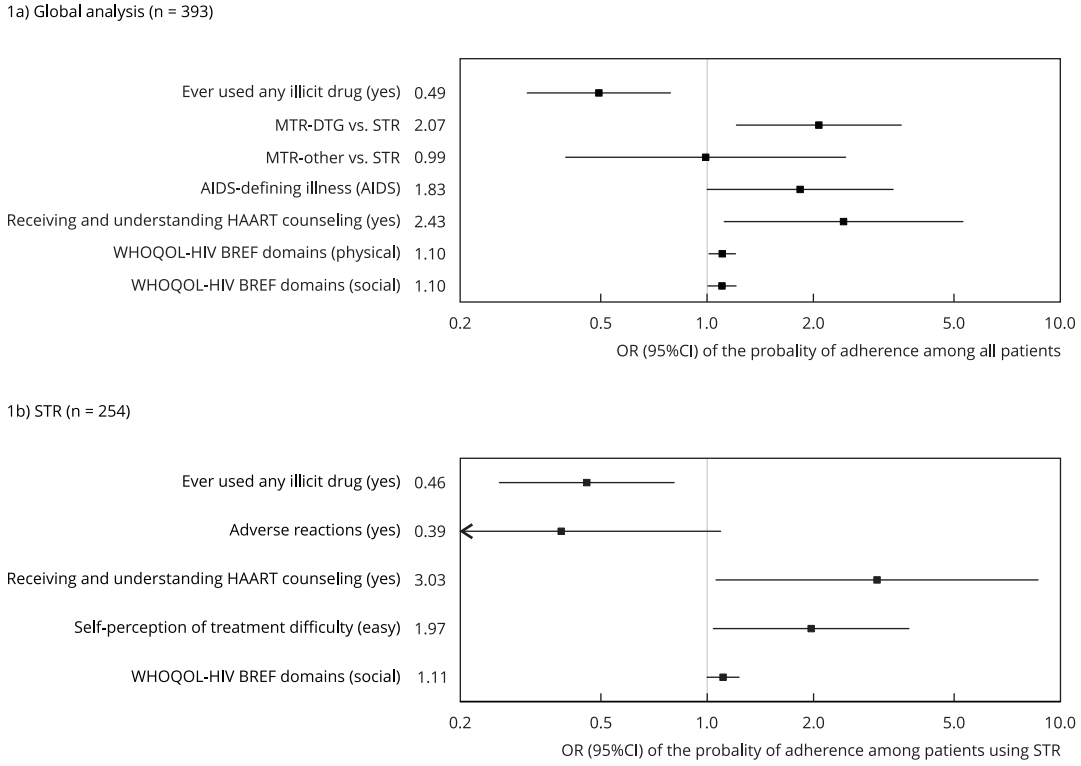
The rate of adherent individuals within the HAART subgroups was lower in the present study when compared to the literature. Studies using self-report scales showed rates of adhesion ranging from 62% to 85.4% for the STR group and from 48.6% to 92.8% for MTR groups [26,27]. However, when a higher cut-off point in the MMAS-8 is used (100%), reported rates can be as lower as 14.2% for STR and 26.9% for MTR [23].

Studies evaluating adherence specifically in MTR-DTG regimens are scarce, and those evaluating HAART regimens of multi-tablet once-daily also reported higher rates of adherent individuals than our study: 65.3% [28] and 68.9% [7]. However, they measured adherence using pharmacy refill records and tablet counts, respectively.

There are plenty of methods to measure adherence and the differences between them impact on the results and its comparability across studies. Indirect methods, like self-report, can be measured

Figure 1

Forest plot of multivariate analysis of adherence to highly active antiretroviral therapy (HAART) according to the antiretroviral regimen.



(continues)

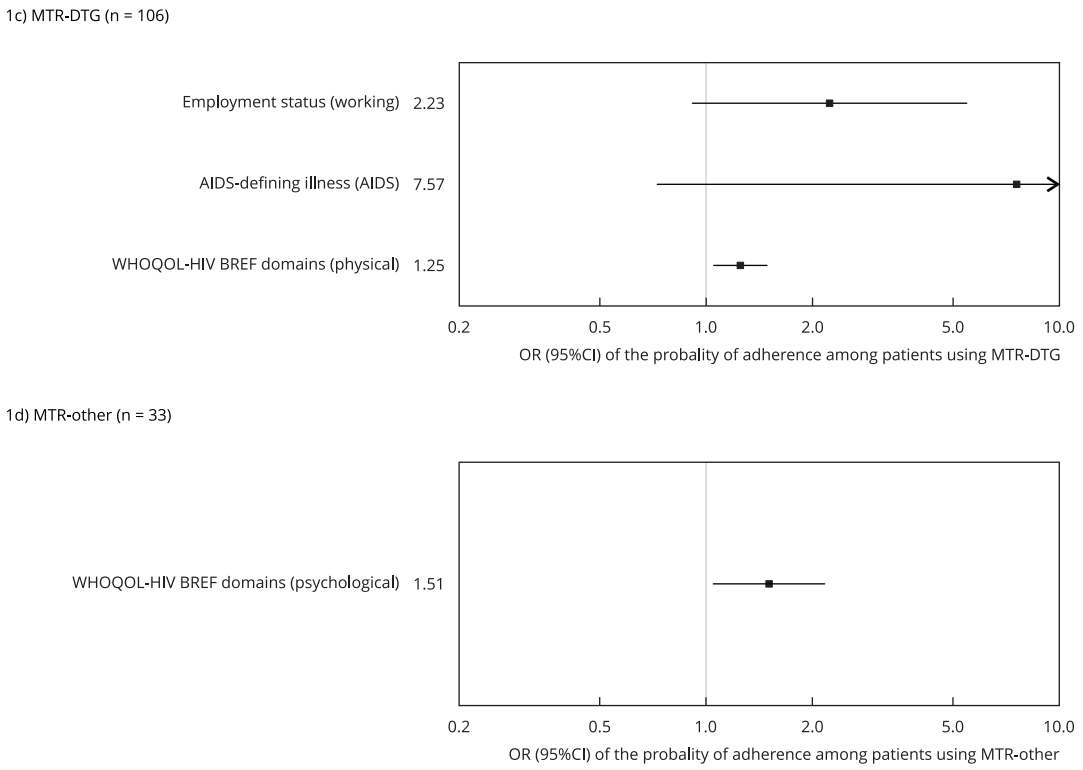
by direct questions to patients or using scales, such as the MMAS-8, the *Visual Analogue Scale* and the *Questionnaire for the Evaluation of Adherence to Antiretroviral Treatment*. Another issue is related to the cut-off points adopted to define adherence. Most studies use a cut-off point up to 95%, while in the present study a more rigorous cut-off point was adopted (100%). Additionally, the specificity of the Brazilian therapeutic regimens, as well as the cultural and sociodemographic characteristics of the population, can explain the variability in the results.

The overall adherence to antiretroviral therapy was influenced by behavioral and lifestyle habits, clinical, HAART and health service-related characteristics and by the quality of life. Garbin et al. [29] found in a literature review a rate of adherence to antiretroviral therapy ranged from 18% to 74.3% among Brazilian states.

There are several studies in the literature reporting better adherence rates among patients using STR when compared to multi-dose MTR [7,8,28,30]. The meta-analysis of Nachega et al. [8] showed better adherence for HAART-naïve patients using once-daily regimens, which included STR and other regimens taken once-daily in the same group, compared to twice-daily regimens. Results for the comparison of STR to once-daily MTR, however, are more heterogeneous, with studies reporting better results to STR or absence of difference among groups [7,28].

Contrastingly, in our study, the MTR once-daily containing DTG showed better results when compared to the STR. Both regimens are used with the "backbone" of TDF/3TC, and bottom line, the comparison of effects are related to the third antiretroviral agent characteristics, such as their pill burden and tolerability. We observed a lower rate of adverse events and a lower proportion of patients

Figure 1 (continued)



95%CI: 95% confidence interval; MTR-DTG: multi-tablet regimen once daily with dolutegravir – TDF/3TC + DTG; MTR-other: multi-tablet multi-dose; OR: odds ratio; STR: single tablet regimen – TDF/3TC/EFV.

having more than five adverse drug reactions among patients in the MTR-DTG group. The profile of adverse events also differenced among groups [31] and may have contributed to increasing the chance of adherence to HAART. Adverse reactions such as dizziness, rashes, and vomiting are common and may interfere negatively with the patient's daily life. Discussing all possible adverse reactions before starting HAART and managing the symptoms are critical for achieving a good adherence. Additionally, individual evaluation of adverse reactions can be useful in the elaboration of strategies to maintain a good adherence [32].

The association between quality of life and adherence is common in the literature, and studies have reported a higher quality of life and its components, such as the capacity of working, social support and psychological status to influence the success of HAART [33]. In our study, patients on MTR-other regimens showed, in general, a worse prognosis compared to other groups, illustrated by the higher rate of advanced disease, a higher number of comorbidities and higher adverse events rate. In addition to lower adherence rates, all these characteristics may affect their social role and self-perception on their health status, reflecting the lower quality of life values among this group.

The quality of the counseling to the patient about their HAART treatment and the good relationship between patient and health professionals also influenced positively the adherence [24,34]. The counseling about medicines help the individual to better understand his/her treatment and this contributes for patients to strive more to follow it correctly. Indeed, individual's perception of their treatment as easy was associated with higher chance of adherence to HAART in the STR subgroup. Previous studies have shown individuals who considered their treatment difficult were 21 times more likely to have inadequate adherence [35].

Another concern is with the use of illicit drugs, as they affected negatively the adherence to HAART in this and in several other studies [27,32]. Some possible strategies to increase adherence include treating the addiction, preparing health professionals to deal with these individuals, and seeking healthier alternatives for coping together with patients [36,37]. Therefore, investing in strategies to improve and broaden the counseling by health professionals is of great importance, since this type of strategy can target simultaneously various factors related to adherence, has low cost, easy implementation and results are achieved in the short to medium term. In addition, health professionals should individually approach patient's self-perception in order to clarify possible doubts and improve their own perception [35].

Low adherence to HAART is a public health issue, as it influences not only the health of each individual but also the overall population living with HIV. In addition to being a major cause of therapeutic failure, it increases the risk of developing drug resistance. The transmission of resistant strains to the initial therapeutic regimens contributes to the bankruptcy of these regimens, leading to negative impacts on public policies and on the health system [38]. Clinically, one of the outcomes of inadequate adherence is the reduction of LT-CD4+ leading to a decreased immunity level, increased risk of opportunistic infections, and possible progression to AIDS. These factors may also result in an increase in the risk of hospitalizations and consequently higher costs to the health system [38,39].

Strategies to achieve adequate HAART adherence include cognitive-behavioral therapy, performed in motivational interviews and followed by educational actions, choice of supporters and medicines reminder devices, such as cell phone alarms and tablet packaging with timers or alarms [40]. Short message service, such as SMS text messaging, also increase adherence compared to standard care and combined interventions resulted in greater overall adherence than isolated interventions [41].

Despite the adherence results, a study with participants of service I showed, at six months, 74.6% of overall viral suppression and 80.6% of viral supression among patients who used STR ($p = 0.04$). Factors independently associated with viral suppression at six months were: (negatively) viral load ≥ 100,000 copies/mL, symptoms of AIDS, longer interval time between diagnosis and initiation of antiretroviral therapy, antiretroviral switching, smoking or current illicit drugs usage; and (positively) category of exposure of men who have sex with men and acherence to HAART [42].

An international cohort study in South Carolina (USA) showed that people using STR achieve viral suppression with adherence levels of 80% or greater, whereas people using MTR require adherence levels of 90% or greater to achieve viral suppression [43].

In Brazil, the Ministry of Health recommends the support of the multi-professional team to the individual, including the implementation of support groups, lectures, activities in waiting rooms, educational activities with the availability of material and actions in partnership with civil society organizations. Furthermore, it is important health professionals to well-inform individuals in a clear way, making sure they understand the information. In addition, it is important to understand patients' beliefs and routines to determine together the best way to achieve adherence [4].

High-quality HIV services must continue to expand in order to maintain and improve the outcomes. Brazil has seen an increase from 83% (in 2015) to 84% (in 2017) in HIV-diagnosis. The portion of people living with HIV on treatment stood at 64% in 2017, 59% of whom were virally suppressed. One major challenge is the sustained programs in the country for reducing the number of new infections among key affected populations [4].

This study has some limitations. The adherence was measured by a self-report scale not specific to HIV. However, this method is fast, easy to apply and is a good predictor of virological failure [44]. Furthermore, several studies used the MMAS-8 to measure HAART adherence [23,24,25,35] and although there is a multiplicity of indirect measures of adherence, none of them is considered a "gold standard". The triangulation of methods increases the validity and reliability of the adherence results. For greater robustness of results and to allow comparisons between them, future research and practice interventions should use a standardized and internationally accepted definition; clearly describing which medicines and methods were used.

In addition, due to the cross-sectional design of the study, it is not possible to establish the temporal relationship between cause and effect. However, we continue to follow up patients to evaluate long-term results and to confirm these findings. Finally, the study's population was selected by non-randomized sampling although we have universal register on the SICLOM.

Conclusion

The overall adherence rate in individual's initiating HAART was low with better results for patients using the dolutegravir once-daily regimen, which is the first-choice regimen currently used in Brazil. Results highlighted the need for intervention strategies to increase adherence to HAART, focusing on health professional's counseling about HAART and substance use. Finally, the interventions performed should be specific and oriented to the HAART-regimen, since different factors affect adherence in each group.

Contributors

T. S. Cardoso was responsible for study design, data extraction, data interpretation, drafting of the manuscript and approval of the final manuscript. J. O. Costa was responsible for data extraction, data analyses, data interpretation, drafting of the manuscript and critical review. E. A. Reis was responsible for data interpretation, critical review, and approval of the final manuscript. M. R. Silveira was responsible for study design, critical review, and approval of the final manuscript. P. F. Bonolo was responsible for study design, data interpretation, and critical review. S. F. Santos was responsible for data interpretation and critical review. M. G. B. Ceccato was responsible for study design, data analyses, data interpretation, critical review, and approval of the final manuscript.

Additional informations

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Resumo

Avaliamos a adesão à terapia antirretroviral (TARV) e fatores associados de acordo com o tipo de esquema em pacientes no início do tratamento em Belo Horizonte, Minas Gerais, Brasil. Mensuramos a adesão com a Escala de Adesão Terapêutica de Morisky*, de oito itens (MMAS-8), e comparamos o uso de tenofovir/lamivudina com efavirenz, um comprimido uma vez ao dia (STR), ou dolutegravir em múltiplos comprimidos uma vez ao dia (MTR-DTG), com outros esquemas com múltiplos comprimidos ao dia (MTR-outros). Conduzimos uma análise de regressão logística multivariada para avaliar os fatores associados à adesão. Foram incluídos 393 pacientes: 254 em uso de STR, 106 MTR-DTG e 33 MTR-outros. A taxa global de adesão foi 44,8% (IC95%: 39,4; 50,1), sendo 50% para MTR-DTG, 43,3% para STR e 39,4% para MTR-outros. A análise multivariada mostrou chances maiores de adesão em pacientes em uso de MTR-DTG, pacientes que haviam recebido e compreendido o aconselhamento sobre o tratamento e pacientes com melhor qualidade de vida. Uso anterior de drogas ilícitas em qualquer período da vida está associada à pior adesão. A adesão global foi baixa, enfatizando a necessidade de estratégias focadas no aconselhamento sobre medicamentos e uso de drogas. A quantidade de comprimidos não foi um problema para pacientes em uso de MTR-DTG uma vez ao dia, os quais alcançaram melhores taxas de adesão.*

HIV; Antirretrovirais; Adesão à Medicação; Autorrelato

Resumen

Evaluamos la adherencia a la terapia antirretroviral altamente activa (TARAA) y sus factores asociados, según el tipo de tratamiento en pacientes que comenzaron su tratamiento en Belo Horizonte, Minas Gerais, Brasil. La adherencia se mensuró por la Escala de Adhesión Terapéutica de Morisky*, de ocho ítems (MMAS-8), y se comparó el uso del "eje" tenofovir/lamivudina, además de un comprimido de efavirenz una vez al día (STR) o dolutegravir con varios comprimidos una vez al día (MTR-DTG), u otros tratamientos con múltiples comprimidos (MTR-otros). Se realizó un análisis multivariado de regresión logística para evaluar los factores asociados a la adherencia. Se incluyeron un total de 393 pacientes, 254 usaron STR, 106 MTR-DTG, y 33 MTR-Otros. La tasa de adherencia general fue de un 44,8% (95%CI: 39,4; 50,1), 50% en el MTR-DTG, 43,3% en el STR y 39,4% en el MTR-otros. El análisis multivariado mostró una probabilidad más alta de adherencia entre pacientes usando MTR-DTG, quienes recibieron y comprendieron las orientaciones acerca de sus tratamientos y los que disfrutaban de una calidad mejor de vida. El consumo previo de drogas ilícitas a lo largo de la vida estuvo asociado con una adherencia más escasa. La adherencia general fue baja y resalta la necesidad de estrategias que se enfoquen en brindar orientación sobre el uso de la medicación y de sustancias. El número de comprimidos no fue un problema para los pacientes que tomaban MTR-DTG una vez al día, que obtuvieron mejores resultados.*

VIH; Antirretrovirales; Cumplimiento de la Medicación; Autoinforme

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