Real-World Characterization of the Portuguese Population Living with HIV who Initiated Raltegravir Based-Regimens: The REALITY Study

Caracterização da População Portuguesa com VIH que Iniciou um Regime Baseado em Raltegravir: O Estudo REALITY

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ABSTRACT

Introduction: Although raltegravir has been available since 2007, data are lacking on the Portuguese population living with HIV who initiated this antiretroviral therapy. Hence, this study aimed to characterize the patients who initiated raltegravir-based regimens between January 2015 and December 2017, on sociodemographics, clinical features, and treatment satisfaction.

Material and Methods: Observational, retrospective, multicentre study conducted at 11 reference sites. Sociodemographic and clinical data were collected retrospectively from hospital medical records. For participants continuing raltegravir at study inclusion, the HIV Treatment Satisfaction Questionnaire was administered to assess satisfaction with raltegravir-based therapy. Descriptive statistics were performed. Treatment-naïve and treatment-experienced subgroups were compared for demographic and clinical variables.

Results: A total of 302 patients were included; mostly men (69.5%) with a mean age of 49 years old. Approximately half of the patients had at least one non-AIDS-related comorbidity at baseline (53.3%), such as hypercholesterolemia, arterial hypertension, diabetes mellitus, and depression. Moreover, 52.3% were treatment-experienced patients with up to two treatments prior to raltegravir. Across the study time points, there was a reduction in the viral load and improvement in CD4 counts in both the treatment-naïve and treatment-experienced subgroups. Continuing users of raltegravir reported high treatment satisfaction (55.4 ± 7.2 points).

Conclusion: Raltegravir-based regimens seem like a valid therapeutic option in heterogeneous populations of HIV-infected patients, in patients with previous ART experience and as part of first-line therapeutic options alongside with the latest generation of drugs from its class.

Keywords: Anti-Retroviral Agents; HIV Infections/complications; HIV Infections/drug therapy; Portugal; Raltegravir Potassium/therapeutic use

RESUMO

Introdução: Apesar de o raltegravir estar disponível desde 2007, os dados na população portuguesa com VIH que iniciou esta terapêutica antirretroviral são escassos. Deste modo, este estudo teve por objetivo caracterizar os doentes que iniciaram um regime terapêutico baseado em raltegravir entre janeiro de 2015 e dezembro de 2017, relativamente a dados sociodemográficos, características clínicas e satisfação com o tratamento.

Material e Métodos: Estudo observacional, retrospetivo, multicêntrico conduzido em 11 centros de referência. Os dados sociodemográficos e clínicos foram recolhidos retrospetivamente nos processos clínicos. Os participantes que continuaram o regime com raltegravir após a inclusão no estudo preencheram o *HIV Treatment Satisfaction Questionnaire* para avaliar a satisfação com a terapêutica. Foram efetuadas análises de estatística descritiva e comparações para as variáveis sociodemográficas e clínicas nos subgrupos de doentes *naïve* de tratamento e de doentes com experiência terapêutica.

Resultados: Foram incluídos 302 doentes, maioritariamente do sexo masculino (69,5%) com idade média de 49 anos. Aproximadamente metade dos doentes tinha pelo menos uma comorbilidade não relacionada com SIDA no início do estudo (53,3%), tais como hipercolesterolemia, hipertensão arterial, diabetes *mellitus* ou depressão. Adicionalmente, 52,3% eram doentes com experiência terapêutica com até dois tratamentos anteriores ao raltegravir. Ao longo do estudo verificou-se uma redução na carga viral e uma melhoria nas contagens de CD4 em ambos os subgrupos de doentes (doentes *naïve* de tratamento e doentes com experiência terapêutica). Os doentes com uso continuado de raltegravir reportaram uma elevada satisfação com o tratamento (55,4 ± 7,2 pontos).

Conclusão: Os regimes terapêuticos baseados em raltegravir parecem ser uma opção terapêutica válida em populações

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heterogéneas de doentes infetados com VIH, em doentes com experiência em ART e como tratamento de primeira linha, em paralelo com outras terapêuticas de última geração.

Palavras-chave: Antirretrovirais; Infecções por VIH/complicações; Infecções por VIH/tratamento farmacológico; Portugal; Raltegravir Potássico/uso terapêutico

INTRODUCTION

The human immunodeficiency virus (HIV) infection is currently a chronic disease, for which new challenges arise, such as the search for life-long, effective, and safe treatments.[1] New available antiretroviral therapies (ART) show similar high efficacy rates in clinical trials.[2] Real-world data can provide a comprehensive characterization of different patients and an understanding of how to achieve an individualized care plan for specific subgroups of HIV-infected individuals.[3,4]

Raltegravir (RAL) is an HIV-1 integrase inhibitor that demonstrates potent antiretroviral activity and well-tolerated oral administration, with few drug-drug interactions.[5,6] Several clinical trials support the efficacy and safety profile in both treatment-naïve and experienced adults infected with HIV-1.[7-13] Real-world cohort studies confirm the effectiveness and tolerability of RAL in clinical practice, and the potential use of this drug in different subsets of patients (e.g., with previous treatment for HIV / non-naive, pregnant, co-infected).[14-16]

Between 1983 and 2019, 61 433 individuals had HIV in Portugal [2020 data from the Directorate-General of Health (DGS)] and, in late 2018, there were 41 305 people living with HIV (prevalence of 0.40%).[17] In this study, we aimed to characterize, for the first time, patients treated with RAL in clinical practice, the sociodemographics, and the satisfaction with treatment among those receiving treatment with RAL. Furthermore, in an exploratory analysis, treatment-naïve and treatment-experienced patients were compared for the viral, immunological, and clinical variables.

MATERIAL AND METHODS

This was an observational, retrospective study conducted at 11 Portuguese reference centers with structured HIV Units in the Portuguese mainland. All study procedures were performed under routine clinical practice. The study was approved by each site's Ethics Committee.

Between July 2018 and April 2019, written informed consent was obtained during a routine medical appointment and patients were included in the study if they were HIV-1, aged ≥ 18 years old at baseline, and initiated RAL between January 2015 and December 2017. Baseline was defined as the time of initiation of RAL-based therapy. Both treatment-naïve and treatment-experienced patients were included. The participant's medical records must have had, at least, the following information: age, sex, date of diagnosis of HIV infection, date of RAL initiation, CD4 counts, and viral load (VL) at baseline. Patients were excluded if enrolled in a clinical trial during the observation period with or without RAL, or if unable/unwilling to comply with study requirements according to the investigator's opinion. In order to minimize selection bias, patients were enrolled in a consecutive manner.

Considering the expected number of patients under treatment with RAL-based regimens (2880 medical records screened), the minimal possible sample established to achieve a precision ≈ 5% for any estimated proportion of the patient's characteristics, with 95% CI, was a sample size of 296 patients. By the time of RAL initiation in this study (between 2015 and 2017), only RAL 400 mg (BID) was available in Portugal. RAL 600 mg was granted reimbursement by the Portuguese medicines agency (INFARMED, I.P.) in December 2018 and, therefore, all study participants were on RAL 400 mg. Treatment switch between RAL formulations was not collected in this study.

Measures

Sociodemographic and clinical characteristics

Sociodemographic and clinical data were collected retrospectively from hospital medical records. Demographics included age at baseline, sex, and country of origin; addictive behaviors included smoking (current or past smoker, or never smoked), diagnosis of chronic alcoholism,[18] and illicit drug use (current or past user, or never used).

Clinical data related with HIV infection covered the following: duration of HIV infection, mode of transmission, CDC stage 1993 Revision[19] (classified in A—clinical categories; B—symptomatic conditions or C—AIDS diagnosis), hepatitis B or C co-infection, plasma HIV RNA (viral load), and CD4 counts at diagnosis (i.e., date of diagnosis of HIV infection), at baseline (i.e., initiation of RAL-based therapy), and at last measurement (i.e., last laboratory value reported in the patients' chart regardless of ART regimen—patients could be or not on RAL). Duration of HIV infection was defined as the time between diagnosis and baseline (i.e., initiation of RAL-based therapy).

Non-AIDS-related comorbidities

Non-AIDS-related comorbidities (NARC) were obtained from the medical records, including hypercholesterolemia, arterial hypertension, anxiety/depression, chronic hepatitis C, diabetes mellitus, nephrolithiasis, emphysema/bronchitis, renal failure, malignancy, osteoporosis, and chronic hepatitis B. The number and type of non-AIDS-related comorbidities were calculated based on the number of patients with at least one reported non-AIDS-related comorbidity (n = 161 patients). These variables were considered of interest based on their high prevalence in the Portuguese population and clinical relevance in the HIV-infected population, as described in a previous population-based study.[20]

Antiretroviral treatment

For treatment-experienced patients, data on previous ART regimens were collected, namely the therapeutic class of last ART, before RAL-based therapy, and the number of

previous treatments. RAL-based regimens were described for treatment duration (i.e., start date to the last visit reporting RAL-based therapy), and continuing use at the study visit.

The number and type of previous ART regimens were calculated based on the number of treatment-experienced patients (n = 199 patients).

Treatment satisfaction with RAL-based regimen

For those patients who were RAL-continuing users, a patient-reported questionnaire was administered during the study visit, to assess the satisfaction with RAL treatment (HIV treatment Satisfaction Questionnaire, HIVTSQs©).[21-23] The Portuguese version of the HIVTSQs© (version 8.4.10) used in this study has been linguistically validated, including review by a clinician and pilot testing in Portuguese patients.

Statistical analysis

All patients fulfilling the selection criteria were included for statistical analysis. Descriptive statistics were performed. Continuous variables were summarized as mean ± standard deviation (SD), median, range, and interquartile range (IQR); categorical variables were summarized as absolute and relative frequencies. CD4 counts were presented by thresholds (≤ 200 cells/mm^3; 201 - 500 cells/mm^3; > 500 cells/mm^3), as well as for VL (≤ 50 copies/mL; > 50 copies/mL).

The HIVTSQs© score derived from two subscales (General Satisfaction and Lifestyle) grouped together to produce the treatment satisfaction total score (range: 0 - 60 points).[20-22] The higher the score, the greater the treatment satisfaction. Internal consistency reliability of the 10-item treatment satisfaction scale (HIVTSQs©) was assessed using Cronbach's alpha coefficient.

As part of the exploratory objectives of this study, treatment-naïve and treatment-experienced subgroups were compared for quantitative variables (CD4 counts, VL) by *t*-test or Mann-Whitney nonparametric test, according to the assumption validations of the statistical test. Comparisons between subgroups regarding categorical variables were tested through Chi-square test or Fisher exact test, when assumptions of Chi-square test were not met.

Associations of independent variables of interest with time to discontinuation of RAL-based regimens were explored based on Kaplan-Meier survival analyses and log rank test. Treatment maintenance was estimated according to RAL treatment duration in months (dependent variable). Hazard ratios (HR) were estimated through Cox regression method to measure the magnitude of risk differences between comparative subgroups. Associations of RAL-based treatment satisfaction (total score and items) with independent variables of interest were assessed by Spearman's rank correlation (quantitative variables) and Mann-Whitney/Kruskal-Wallis (categorical variables).

No imputation of missing data was performed. All comparisons were two-tailed and statistical significance was set at 5%. All analyses were conducted with SAS software (version 9.4; SAS Institute Inc, Cary, USA).

RESULTS

Sociodemographic characteristics

Table 1 summarizes the baseline sociodemographics of the 302 patients included in this study. At baseline, 69.5% patients were males, with a mean age of 49 years;-and approximately half of the patients were above 50 years old (47.0%).

Non-AIDS-related comorbidities

Percentage of NARC was determined in the group of patients reporting any baseline comorbidity (n = 161) and in all study participants (n = 302). More than half of the patients (53.3%) had at least one NARC at baseline (time of initiation of RAL for each patient) (Fig. 1A).

Among those patients who reported baseline comorbidities (n = 161), the most frequent were hypercholesterolemia (44.1%), arterial hypertension (42.2%), diabetes mellitus (17.4%), and depression (17.4%). The same pattern was observed for baseline comorbidities in all participants (n = 302): hypercholesterolemia (23.5%), arterial hypertension (22.5%), diabetes mellitus (9.3%), and depression (9.3%).

Renal failure was also common (11.8% in patients with any comorbidity and 6.3% in all participants). Other comorbidities were described in 70 patients (43.5% of patients with any comorbidity and 23.2% of all participants), including chronic hepatitis C (three patients), cirrhosis (four patients), epilepsy (four patients), and obesity (six patients). Participants with any comorbidity had a mean of 2.0 comorbidities, while 50 reported three or more comorbidities (Fig. 1B).

Clinical HIV characteristics

Clinical characteristics related with HIV infection were described for all study time points (Table 2). The main transmission mode was heterosexual sex (58.0%), followed by men who have sex with men (MSM, 23.0%), and intravenous drug use (IDU, 18.0%). At diagnosis, most patients were at CDC stage A (68.7%). Additionally, 57.3% had a late diagnosis (i.e., CD4 counts < 350 cells/mm^3). Plasma HIV RNA levels (viral load) decreased to viral suppression in most patients (96.0% with ≤ 50 copies/mL at last measurement). The CD4 count increased from diagnosis until last measurement, with 24.8% of the patients having > 500 cells/mm^3 at diagnosis, followed by 46.7% at baseline, and 67.5% at last measurement. Most participants reported no hepatitis B or C co-infection throughout the study time points.

Antiretroviral treatment

Overall, 103 patients (34.1%) were treatment-naïve and 199 (65.9%) were treatment-experienced before initiation of RAL-based therapy. Fig. 2 depicts the number and therapeutic class of last ART. Protease inhibitors (PI)-based therapy (50.8%) and non-nucleoside reverse transcriptase inhibitors (NNRTI)-based therapy (40.2%) were the most

Table 1 – Sociodemographic characteristics of study participants at baseline

Sociodemographic characteristics	n (302)
Sex, n (%)	
Male	210 (69.5%)
Female	92 (30.5%)
Age at baseline*, years	
Mean ± SD	49.1 ± 12.7
Median (min. – max.)	48.0 (19.0 – 92.0)
IQR (Q3 – Q1)	16.0 (57.0 – 41.0)
Geographic origin, n (%)	
Portugal	251 (83.1%)
Brazil	12 (4.0%)
Cape Verde	12 (4.0%)
Other	27 (8.9%)
Smoking status, n (%)	
Current smoker	110 (39.6%)
Former smoker	45 (16.2%)
Never smoker	123 (44.2%)
Unknown	24
Diagnosis of chronic alcoholism, n (%)	
Yes	20 (6.6%)
No	282 (93.4%)
If yes, duration of chronic alcoholism, years (n = 14)	
Mean ± SD	8.6 ± 6.1
Median (min. – max.)	8.0 (0.1 – 17.8)
Missing values	6
Illicit drug use, n (%)	
Never used	230 (76.2%)
Past use	65 (21.5%)
Current use	7 (2.3%)
If past use, substance†, n (%)	
Heroin	50 (76.9%)
Cocaine	32 (49.2%)
Cannabis	9 (13.8%)
Ecstasy	3 (4.6%)
LSD	1 (1.5%)
Other	4 (6.2%)
If current use, substance*, n (%)	
Cocaine	4 (57.1%)
Cannabis	3 (42.9%)
Heroin	2 (28.6%)
Ecstasy	1 (14.3%)
LSD	1 (14.3%)

min.: minimum; max.: maximum: LSD: lysergic acid diethylamide; SD: standard deviation
*: baseline was defined as the time of initiation of RAL-based therapy
†: patients could report more than one option

common ART classes prior to RAL (Fig. 2A). For treatment-experienced patients, the mean duration of previous ART regimens was 4.2 ± 3.2 years (median: 3.7; range: 0.003 - 14.9 years). The number of previous ART regimens ranged between 1 and 11, and 52.3% of the patients received up to two ART regimens (Fig. 2B).

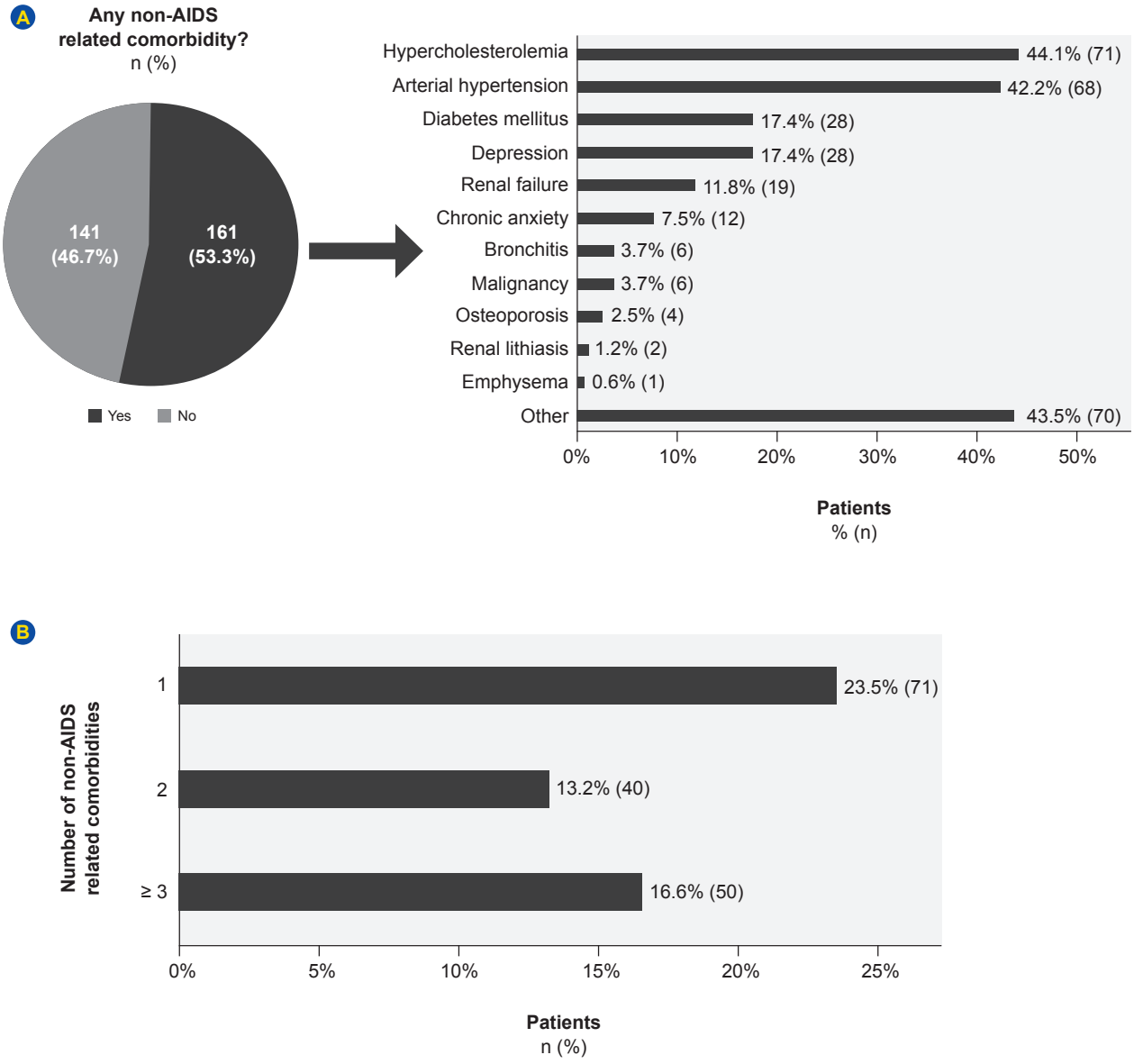

Figure 1 – Non-AIDS-related comorbidities of study participants at baseline: (A) Type of Non-AIDS-related comorbidities; (B) Number of Non-AIDS-related comorbidities

The median time between diagnosis and initiation of the first ART regimen was 6.8 years (i.e., 82.0 months). Most participants (80.8%; 244/302) continued to take RAL at the inclusion visit and the median duration of RAL-based therapies was 2.1 years, considering the time of the study visit as the cut-off.

Treatment satisfaction with RAL-based regimen

In our study, Cronbach's alpha coefficient showed an excellent internal consistency (> 0.9)[24] for reliability of the total score (0.9175). Participants who continued RAL-based therapies at the inclusion visit reported a high satisfaction with a total mean score of treatment satisfaction of 55.4 ± 7.2 points.

Treatment-naïve *versus* treatment-experienced patients

Treatment-experienced patients had a higher median age than treatment-naïve patients (50 years *vs* 43 years, $p < 0.0001$) (S1 Table in Appendix 1: https://www.actamedica-portuguesa.com/revista/index.php/amp/article/view/16785/Appendix_01.pdf).

HIV infection-related characteristics were also described for the two subgroups (Table 3). As expected, treatment-naïve patients had a shorter median duration of HIV infection that was statistically significant, compared to treatment-experienced patients (0.21 years *vs* 12.37 years, $p < 0.0001$). Furthermore, 75.8% of treatment-naïve and 64.8% of treatment-experienced patients were diagnosed at CDC stage A ($p = 0.036$). The proportion of non-co-infected patients at baseline was lower in the treatment-experienced subgroup than in the treatment-naïve subgroup (78.2% *vs* 92.2%, $p = 0.009$). At baseline (RAL initiation), treatment-naïve patients showed a lower median value of CD4 count (336.0 cells/mm^3 *vs* 573.0 cells/mm^3, $p < 0.0001$) and all had a

Table 2 – Clinical characteristics associated with HIV infection, at diagnosis, baseline (RAL initiation) and last measurement

Clinical characteristics associated with HIV infection	At diagnosis*	At baseline†	Last measurement§
Duration of HIV infection at baseline, years			
n	302	-	-
Mean ± SD	8.5 ± 7.5		
Median (min. – max.)	8.0 (0.0 – 28.5)	-	-
IQR (Q3 – Q1)	14.2 (14.7 – 0.5)	-	-
Mode of transmission, n (%)			
Men who have sex with men (MSM)	69 (23.0%)	-	-
Heterosexual sex	174 (58.0%)	-	-
Intravenous drug use (IDU)	54 (18.0%)	-	-
Parenteral	1 (0.3%)		
Other	2 (0.7%)		
Total	300	-	-
Unknown	2	-	-
CDC HIV stage of disease, n (%)			
A	189 (68.7%)	-	-
B	33 (12.0%)	-	-
C	53 (19.3%)	-	-
Total	275	-	-
Unknown	27	-	-
CD4 counts, cells/mm^3			
n	262	302	302
≤ 200 cells/mm^3, n (%)	96 (36.6%)	52 (17.2%)	13 (4.3%)
201 - 500 cells/mm^3, n (%)	101 (38.5%)	109 (36.1%)	85 (28.1%)
> 500 cells/mm^3, n (%)	65 (24.8%)	141 (46.7%)	204 (67.5%)
Late diagnosis (< 350 cells/mm^3)	150 (57.3%)	-	-
Non-late diagnosis (≥ 350 cells/mm^3)	112 (42.7%)	-	-
Plasma HIV – RNA, viral load, copies/mL			
n	238	302	302
≤ 50 copies/mL, n (%)	2 (0.8%)	154 (51.0%)	290 (96.0%)
> 50 copies/mL, n (%)	236 (99.2%)	148 (49.0%)	12 (4.0%)
Co-infection, n (%)			
Hepatitis B	8 (2.7%)	8 (2.7%)	8 (2.7%)
Hepatitis C	58 (19.7%)	43 (14.4%)	12 (4.0%)
No co-infection	228 (77.6%)	248 (82.9%)	279 (93.3%)
Unknown	8	3	3

min.: minimum; max.: maximum; IDU: intravenous drug use; IQR: interquartile range; HIV: human immunodeficiency virus; MSM: men who have sex with men; SD: standard deviation
*: diagnosis was defined as the date of diagnosis of HIV infection.
†: baseline was defined as the time of initiation of Raltegravir-based therapy.
§: last measurement was defined as the last laboratory value reported in patient's chart, regardless of the antiretroviral regimen (patients could or not be on RAL).

detectable VL, compared to treatment-experienced patients. At diagnosis and last measurement, no statistically significant differences were observed between the two subgroups.

The mean duration of RAL-based therapy was very similar between treatment-naïve and treatment-experienced patients [25.0 vs. 25.5 months, $p = 0.747$ (*t*-test)].

The proportion of treatment-naïve patients with no comorbidities was significantly higher than for the treatment-experienced subgroup (63.1% *vs* 38.2%; $p = 0.0001$). Moreover, the median number of comorbidities was lower in treatment-naïve compared to treatment-experienced patients (1 NARC *vs* 2 NARCs, $p = 0.0077$) (S2 Table in Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/16785/Appendix_01.pdf). However, a statistically significant higher proportion of patients with hypercholesterolemia was found in the group of treatment-experienced patients (48.8% *vs* 28.9% in treatment-naïve patients, $p = 0.0314$).

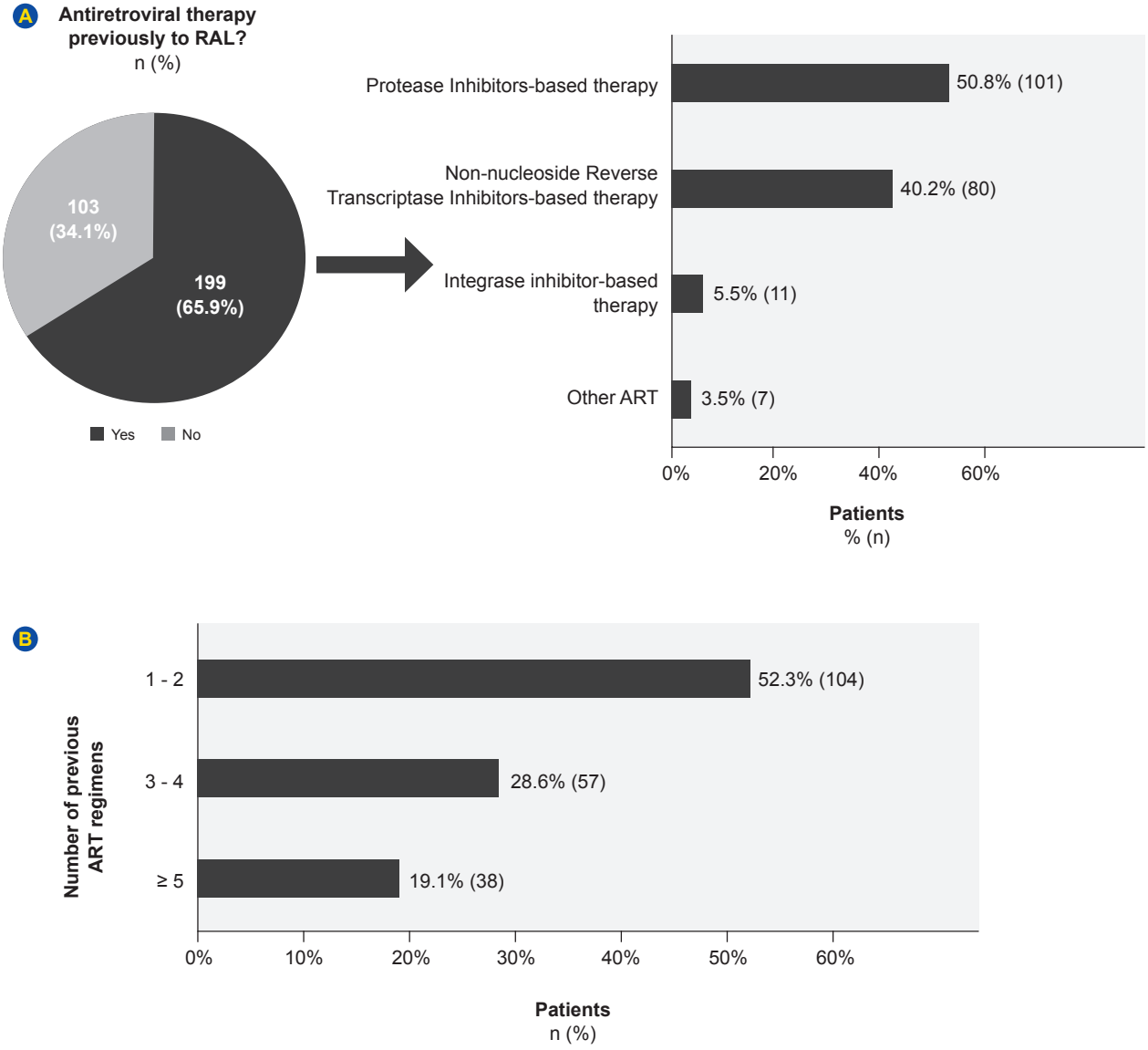

Figure 2 – Characteristics of previous ART regimens in treatment-experienced patients: (A) Type of ART regimen; (B) Number of ART regimens

Associations of independent variables of interest with time to discontinuation of RAL-based treatment and with RAL-based treatment satisfaction

The associations of time to discontinuation of RAL-based regimens and treatment satisfaction of RAL-continuing users assessed for independent variables are shown in Appendix 1, S3 and S4 Tables, respectively (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/16785/Appendix_01.pdf).

Kaplan-Meier estimates for treatment maintenance at 48 months were determined based on the proportion of patients who continued RAL-based regimens. The results suggested that patients with longer time between previous ART regimen and RAL initiation had a slightly higher risk of discontinuation [HR = 1.016, (95%CI: 1.002 to 1.030)], meaning an increase of 1.6% per month in the time between last ART and initiation of RAL therapy.

Significant differences were found for score items in subgroups according to sex, viral load at baseline and co-infection (S5 to S7 Tables in Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/16785/Appendix_01.pdf).

DISCUSSION

The REALITY study characterized a large and representative sample of Portuguese HIV-infected patients who initiated RAL-based regimens, between January 2015 and December 2017, and investigated potential differences in specific subgroups. Almost half of the participants were aged 50 years old, and most were born in Portugal (83.1%). As expected, most patients were men (69.5%); however, the proportion of HIV-infected women in this study was higher than that in most EU/EEA countries in 2019.[25] More than half of the patients were current or past smokers (55.8%)

Table 3 – HIV infection characteristics of treatment-naïve versus treatment-experienced patients

Clinical characteristics associated with HIV infection	Treatment-naïve patients (n = 103)	Treatment-experienced patients (n = 199)	*p*-value
Duration of HIV infection, years			
n	103	199	MW: < 0.0001
Median (min – max)	0.2 (0.0 – 15.1)	12.4 (0.1 – 28.5)	
IQR (Q3 – Q1)	0.7 (0.8 – 0.1)	9.9 (17.2 – 7.3)	
Missing values	206	398	
CDC HIV stage of disease, n (%)			
A	75 (75.8%)	114 (64.8%)	CS: 0.0364
B	13 (13.1%)	20 (11.4%)	
C	11 (11.1%)	42 (23.9%)	
Total	99	176	
CD4 counts, at diagnosis* , cells/mm^3			
Median (min. – max.)	336.0 (6.0 – 1621.0)	286.0 (0.0 - 1165.0)	MW: 0.0511
≤ 200 cells/mm^3, n (%)	28 (29.5%)	68 (40.7%)	CS: 0.1621
201 - 500 cells/mm^3, n (%)	39 (41.1%)	62 (37.1%)	
> 500 cells/mm^3, n (%)	28 (29.5%)	37 (22.2%)	
Missing values	8	32	
Late diagnosis (< 350 cells/mm^3)	50 (52.6%)	100 (59.9%)	CS: 0.2542
Non-late diagnosis (≥ 350 cells/mm^3)	45 (47.4%)	67 (40.1%)	
CD4 counts, at baseline†, cells/mm^3			
Median (min. – max.)	336.0 (6.0 – 1147.0)	573.0 (2.0 – 2067.0)	TT: < 0.0001
≤ 200 cells/mm^3, n (%)	29 (28.2%)	23 (11.6%)	CS: < 0.0001
201 - 500 cells/mm^3, n (%)	46 (44.7%)	63 (31.7%)	
> 500 cells/mm^3, n (%)	28 (27.2%)	113 (56.8%)	
CD4 counts, last measurement§, cells/mm^3			
Median (min. – max.)	641.0 (136.0 – 1598.0)	675.0 (43.0 – 2060.0)	MW: 0.6655
≤ 200 cells/mm^3, n (%)	2 (1.9%)	11 (5.5%)	CS: 0.2643
201 - 500 cells/mm^3, n (%)	27 (26.2%)	58 (29.1%)	
> 500 cells/mm^3, n (%)	74 (71.8%)	130 (65.3%)	
Plasma HIV – RNA, viral load, at diagnosis*, copies/mL			
Median (min. – max.)	96144.0 (94.0 – 7795576)	56881.0 (50.0 – 5000000)	MW: 0.1403
≤ 50 copies/mL, n (%)	1 (1.1%)	1 (0.7%)	FS: > 0.9999
> 50 copies/mL, n (%)	94 (98.9%)	142 (99.3%)	
Missing values	10	61	
Plasma HIV – RNA, viral load, at baseline†, copies/mL			
Median (min. – max.)	88877.0 (156.0 – 7795576)	417.0 (0.0 – 5606415)	MW < 0.0001
≤ 50 copies/mL, n (%)	0 (0.0%)	154 (77.4%)	CS: < 0.0001
> 50 copies/mL, n (%)	103 (100.0%)	45 (22.6%)	
Missing values	1	130	
Plasma HIV – RNA, viral load, last measurement§, copies/mL			
Median (min. – max.)	31.0 (0.0 – 197.0)	26.5 (0.0 – 137000.0)	MW: 0.8828
≤ 50 copies/mL, n (%)	98 (95.1%)	192 (96.5%)	FS: 0.5510
> 50 copies/mL, n (%)	5 (4.9%)	7 (3.5%)	
Missing values	84	169	

min.: minimum; max.: maximum; CS: Chi-square test; FS: Fisher exact test; HIV: human immunodeficiency virus; IQR: interquartile range; MW: Mann-Whitney test; TT: T-test
*: diagnosis was defined as the date of diagnosis of HIV infection.
†: baseline was defined as the time of initiation of Raltegravir-based therapy.
§: last measurement was defined as the last laboratory value reported in patient's chart regardless of the antiretroviral regimen (patients could or not be on RAL).

but reported low percentages of current or past history of drug or alcohol disorders. The AGING POSITIVE study — an observational study conducted in the Portuguese HIV-infected population — reported similar rates of chronic alcoholism (7.7%), past or current use of tobacco (47.6%) and of illicit drugs (17.2%).[20] The rate of current smokers in HIV-infected patients is two to three times higher than in the general population, increasing the risk of NARC.[26]

In our study population, the most common comorbidities were hypercholesterolemia, arterial hypertension, diabetes mellitus, and depression. Most participants had no hepatitis B or C co-infection during the study period, which could have reflected the high cure rates in HCV patients resulting from the treatment program implemented in Portugal.[27] The AGING POSITIVE study described consistent results on the comorbidities of Portuguese HIV-infected patients, which are comparable to those reported here and for the general population.[20] The proportion of patients with hypercholesterolemia was lower in the REALITY study when considering the overall study population (23.5% *vs* 60% in the AGING POSITIVE study).[20] This proportion is closer to that described in HIV-infected populations from other regions, such as Brazil and the United States (US).[28,29] However, it should be highlighted that participants of the AGING POSITIVE study were older (all patients were ≥ 50 years) and had longer duration of HIV infection.[20]

The MSM mode of transmission in Portuguese patients is reported to be low (9% - 18%),[17,20] compared to those from other European studies (31% - 41%).[15,30,31] Low MSM transmission may be associated with cultural factors and is less common in older HIV-infected individuals. Heterosexual transmission appears to be more frequent in men who present high-risk behaviours (e.g., IDU or commercial sex) and travel abroad.[25,32] This transmission route is also the most common one in patients with late HIV diagnosis (CD4 counts < 350 cells/mm^3).[25] In fact, 57.3% of the study participants had a late HIV diagnosis. Both the European Centre for Disease Prevention and Control (ECDC) annual report for Europe and national data from Portugal's Directorate-General of Health (DGS) in 2019 agreed in determining that almost half of the patients had a late HIV diagnosis (49.7% in EU/EEA and in Portugal).[17,25] The median time between diagnosis and initiation of the first ART regimen was approximately seven years. In our study, 81 patients had a delay of more than eight years between HIV diagnosis and the start of ART. This gap has been associated with multiple patient-level reasons (e.g., patient's concerns about treatment, prolonged adjustment periods, or IDU),[33] or structural reasons (e.g., access barriers, lower socioeconomic status), especially among migrants.[34] Although these patients were diagnosed with HIV many years ago - between 1987 and 2006 - and were later referred for treatment, early interventions in patient perception and decision to start ART are still of foremost importance nowadays. In 2015, clinical guidelines were amended to recommend treatment of all patients regardless of the infection stage.[35] Therefore, knowing that over 50% of the study patients were treatment-experienced and the duration of the infection is long, this might also help explain the delay in treatment initiation.

A reduction in plasma HIV RNA and an improvement in CD4 counts were observed from diagnosis until last measurement.[36] Two patients had reported undetectable VL at diagnosis. One of these patients was treatment-naïve and was born in another country, while the second was treatment-experienced and had a VL of 50 copies/mL at diagnosis. Both patients had CD4 counts > 500 cells/mm^3 and it took several months before initiating ART. These cases could be either patients who were already receiving HIV treatment at another clinic (and whose information was not transferred to the current centre), or HIV controllers that maintain suppressed VL for years without ART.[37,38]

Approximately half of the treatment-experienced patients (52.3%) received up to two prior treatments, with the previous ART regimen lasting, on average, 4.2 years. PI-based therapies (50.8%) and NNRTI-based therapies (40.2%) were the most frequently administered ART, as reported in the AGING POSITIVE study.[20] A similar pattern in ART prescribing was found for other large population-based studies in the US and Europe (e.g., UK, Germany, and France).[14,15,31,39,40] Switching from a prot-based to a RAL-based regimen has been associated with a decrease in plasma lipids (e.g., total cholesterol, LDL cholesterol, and triglycerides), which might confer long-term cardiovascular protection to patients.[41] This effect of treatment switch was also described in a cohort of older HIV-infected patients (aged 60 years and older).[42] Furthermore, as regimens containing tenofovir alafenamide (TAF) were only available with reimbursement in Portugal by December 2017, it is unlikely that the patients were taking this drug known to increase lipid levels.

Around 81% of the patients were RAL-continuing users at the time of the inclusion visit. The HIVTSQs© was administered to these participants, who reported high satisfaction with RAL-based therapy (55.4 ± 7.2 points). The well-established low drug-drug interaction profile[43] and tolerability of RAL might explain the satisfaction for this regimen in a setting of high burden of comorbidities and co-medications. As patients could have started other ART regimens several weeks before study inclusion, satisfaction with RAL was not assessed in patients who discontinued this therapy. However, this fact might have contributed to the high level of satisfaction obtained with RAL in this study. Reasons for discontinuing RAL-based regimens were also not collected in this study; nonetheless, those reasons most frequently reported for RAL switch are patient/physician choice and treatment simplification.[44,45] Considering that RAL 600 mg was approved in Portugal in December 2018, it is unlikely that participants switched from RAL 400 mg to 600 mg during the recruitment period (July 2018 – April 2019). Although this information was not collected, most participants were expected to be on RAL 400 mg (BID) at study inclusion.

As expected, treatment-experienced patients were older and had longer duration of HIV infection than treatment-naïve patients. More patients in the treatment-experienced

subgroup had at least one NARC at baseline. At RAL initiation, treatment-experienced patients had higher CD4 counts and a higher proportion of undetectable VL than treatment-naïve patients ($p < 0.0001$). And, at the last measurement, both subgroups had a CD4 count increase and a reduction of viral load. These similar clinical outcomes appear to support the effect of RAL-based regimens on immune restoration (particularly in treatment-naïve patients),[9] considering that most patients (80.8%) were RAL-continuing users. In other real-world studies evaluating RAL-based regimens, increasing CD4 counts[16,46] and high rates of viral suppression (over 80%)[14] were observed in both groups.

Exploratory analyses suggest that a longer time between discontinuation of previous ART regimens and initiation of RAL might increase the risk of treatment discontinuation. Patients with a history of ART interruption were reported to have the highest rates of RAL discontinuation (23.7%), while those with suppressed VL at baseline had the lowest (13.2%).[47] However, several other patient-related factors –such as treatment perception and expectations or personal reasons– can lead to early treatment discontinuation.[48]

The main limitations of this study are related with its observational and retrospective design, relying mainly on routine clinical records with laboratory results (viral load and CD4 count) collected by different laboratories. Of notice, the HIVTSQs® was only applied as a cross-sectional survey instrument in order to assess the level of satisfaction in patients who were continuing users of RAL at the inclusion visit. Therefore, treatment satisfaction for those who discontinued RAL prior to the enrolment period could not be appraised. To overcome these limitations, prospective studies should be conducted to assess causal relationships between patient-related factors, adherence to ART, treatment satisfaction over time and discontinuation rates among specific subgroups.

CONCLUSION

RAL-based regimens are a valid therapeutic option in heterogeneous populations of HIV-infected patients. To the best of our knowledge this is the first study in Portugal to evaluate real world data in patients treated with RAL and satisfaction among those remaining on RAL. This therapy can be used in patients with previous ART experience and as part of first-line therapeutic options considered in clinical guidelines,[49] alongside with the latest generation of drugs from its class.

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AUTHORS CONTRIBUTION

RS, KM, FM, NM, AC, RP, AZ, JM, IN, JO, PP, RCA, ACM, PC, LP, JA: All the authors had an equal contribution to the literature research, draft and distribution of the questionnaire, analysis of the results and draft of the paper.

PROTECTION OF HUMANS AND ANIMALS

The authors have followed the protocols of their work center on the publication of data. The data was anonymized and none of the authors had access to patient identification. The study was conducted in accordance with the Helsinki Declaration updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

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