

# MILD SELF-DECLARED SIDE EFFECTS OF BOOSTED DARUNAVIR ASSOCIATED WITH OTHER ANTIRETROVIRALS IN ROMANIAN HIV-1 INFECTED PATIENTS

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## ABSTRACT

**Introduction.** Antiretroviral therapy (ART) is used in human immunodeficiency virus (HIV)-infected patients, to suppress viral replication and slow disease progression. The side effects of ART, milder or more serious, frequently occur, thus the main challenge for specialists is to find a balance between the benefits of long-term viremia suppression and the risks of toxicity.

**The objective of the study** was to compare the frequency of mild side effects after administration of a regimen containing darunavir (DRV) boosted with ritonavir (RTV) (DRV/r 600 mg/100 mg, twice daily), vs DRV boosted with cobicistat (COBI) (DRV/c - 800 mg/150 mg, once a day) and perform a profile of the patient at risk of developing these types of adverse reactions during ARV treatment.

**Materials and methods.** 462 patients were enrolled in the study and divided into two groups: 384 received DRV/r, and 78 DRV/c. This was a retrospective,

## RÉSUMÉ

**Effets secondaires légers auto déclarés du darunavir renforcé associés à d'autres antirétroviraux chez les patients roumaines infectés par le HIV-1**

**Introduction.** La thérapie antirétrovirale (ART) est utilisée chez les patients infectés par le virus de l'immunodéficience humaine (HIV), pour supprimer la réplication virale et ralentir la progression de la maladie. Les effets secondaires de l'ART, plus légers ou plus graves, surviennent fréquemment, ainsi le principal défi pour les spécialistes est de trouver un équilibre entre les avantages de la suppression de la virémie à long terme et les risques de toxicité.

**L'objectif de l'étude** était de comparer la fréquence des effets secondaires légers après l'administration d'un schéma thérapeutique contenant du darunavir (DRV) boosté par du ritonavir (RTV) (DRV/r 600 mg/100 mg, deux fois par jour), vs DRV boosté par du cobicistat (

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non-interventional study using the database of the National Institute of Infectious Diseases “Prof. Dr. Matei Bals”, Bucharest, Romania. The self-declared mild side effects were collected from patients’ medical files and a comparison between the frequency of these in the two groups have been made. The main self-declared mild side effect was statistically correlated with the characteristic parameters of the cohort.

**Results.** The statistical description of the most frequent self-declared mild side effects in the two groups showed that all parameters were found in a greater proportion in DRV/r group than in DRV/c group, with a statistically significant difference of  $p < 0.05$ . Myalgia and sleep disorders correlate strongly positive ( $p < 0.01$ ) with age, and fatigue correlates strongly positive with age and with number of ARV regimens ( $p < 0.01$ ), and positively with pills’ burden ( $p < 0.05$ ).

**Conclusions.** The results of this study demonstrated that ART regimens containing DRV/c have a higher tolerability than those containing DRV/r. They also emphasize the importance of the management of mild self-declared side effects, to increase patients’ adherence to treatment.

**Keywords:** antiretroviral therapy, darunavir, ritonavir, cobicistat, mild side reactions.

**List of abbreviations:**

ADRs – adverse drug reactions  
AIDS – acquired immunodeficiency syndrome  
ART – antiretroviral therapy  
ARV – antiretroviral drug (antiretroviral)  
COBI – cobicistat  
CYP450 – P450 cytochrome  
DRV – darunavir  
EI – entry inhibitor  
HIV – human immunodeficiency virus  
HIV-1 – human immunodeficiency virus, type 1  
II – integrase inhibitor  
NRTI – nucleoside/nucleotide reverse transcriptase inhibitors  
NNRTI – non-nucleoside reverse transcriptase inhibitor  
PI – protease inhibitor  
RNA – ribonucleic acid  
RTV – ritonavir  
SMPC – summary of product characteristics

COBI) (DRV/c – 800 mg/150 mg, une fois par jour) et réaliser un profil du patient à risque de développer ces types d’effets indésirables au cours du traitement ARV.

**Matériels et méthodes.** 462 patients ont été inclus dans l’étude et divisés en deux groupes : 384 ont reçu le DRV/r et 78 DRV/c. Il s’agissait d’une étude rétrospective non interventionnelle utilisant la base de données de l’Institut National des Maladies Infectieuses «Prof. Dr Matei Bals», Bucarest, Roumanie. Les effets secondaires légers autodéclarés ont été collectés à partir des dossiers médicaux des patients et une comparaison entre leur fréquence dans les deux groupes a été effectuée. Le principal effet secondaire léger auto-déclaré était statistiquement corrélé aux paramètres caractéristiques de la cohorte.

**Résultats.** La description statistique des effets secondaires légers autodéclarés les plus fréquents dans les deux groupes a montré que tous les paramètres étaient retrouvés en plus grande proportion dans le groupe DRV/r que dans le groupe DRV/c, avec une différence statistiquement significative de  $p < 0,05$ . La myalgie et les troubles du sommeil sont fortement corrélés positivement ( $p < 0,01$ ) avec l’âge, et la fatigue est fortement corrélée positivement avec l’âge et avec le nombre de schémas ARV ( $p < 0,01$ ), et positivement avec la charge de pilules ( $p < 0,05$ ).

**Conclusions.** Les résultats de cette étude ont démontré que les schémas thérapeutiques antirétroviraux contenant du DRV/c ont une tolérance plus élevée que ceux contenant du DRV/r. Ils soulignent également l’importance de la gestion des effets secondaires légers auto-déclarés, pour augmenter l’adhésion des patients au traitement.

**Mots-clés:** thérapie antirétrovirale, darunavir, ritonavir, cobicistat, effets secondaires bénins.

## INTRODUCTION

Antiretroviral therapy (ART) is an aggressive treatment strategy intended to suppress viral replication and slow disease progression of human immunodeficiency virus (HIV). It involves combinations of multiple antiretroviral drugs (ARV), most commonly 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI). ART has revolutionized the treatment and prognosis of HIV-infected patients, delaying the progression to AIDS and reducing transmission, mortality, and rates of opportunistic infections. However, the side effects of ART, milder or more serious, are a common problem faced by specialists. The treatment of HIV infection has to find the balance between the benefits of long-term viremia suppression and the risks of toxicity. Due to side effects, more than half of patients change the regimen during the first months of treatment, but also later on, reaching dozens of regimens throughout their lives, until there are no longer therapeutic options. About 20% of patients refuse to start ART because of fear of side effects<sup>1</sup>.

The adoption of fixed-dose combinations and single tablet regimens plays a crucial role in achieving patient adherence and compliance to antiretroviral therapy<sup>2</sup>.

Darunavir (DRV) is very effective for therapy-experienced patients with limited options, due to its impressive potency in the presence of PI-resistance mutations<sup>3</sup>. It belongs to the protease inhibitors (PI) class, cornerstone of antiretroviral regimens, which have contributed to therapeutic success. Many studies have demonstrated the effectiveness of DRV against HIV-1 and this antiretroviral drug has become an important component of ART. It has a high affinity for the HIV-1 protease, binds strongly to it, forming a stable complex due to flexible conformation and skeletal interactions<sup>4</sup>.

In Romania, PI are used in combination with low doses of pharmacokinetic enhancers, ritonavir (RTV) 100 mg or cobicistat (COBI) 150 mg as first-line agents in regimens for naive and experienced HIV-positive patients. Pharmacokinetic enhancers increase the plasma concentration of DRV, making it more effective. Combined regimens increase also the tolerability by maintaining the plasma concentration in the effective area, without fluctuations exceeding C<sub>max</sub> value, which would lead to drug-toxicity reactions. The patient's adherence with the dosage, by reducing the number of daily administrations, is added. Food restrictions are also reduced.

RTV (in low dose of 100/ 200 mg) was the first enzyme inhibitor used to enhance an PI<sup>5</sup>. RTV strongly inhibits cytochrome P450 (CYP450) at the intestinal and hepatic level, the 3A4 isomorph and the glycoprotein P, increasing the elimination half-life and the absorption of the DRV, when co-administrated. It has its own antiretroviral activity, being both an inhibitor and an enzyme inducer. This results in disadvantages such as the development of resistant strains and increased risk of side effects. The latter are caused by the molecule itself but are also related to drug-drug interactions. Furthermore, the tolerability problems of RTV have already been demonstrated in several studies<sup>6</sup>.

The RTV's disadvantages led to the development of another enhancer, cobicistat (COBI), a more selective structural analogue of RTV, an enzyme inhibitor only, with no antiretroviral activity of its own. Another major advantage with direct consequences in patients' adherence is that the DRV was co-formulated with COBI in fixed dose, as a single tablet (DRV/c - 800 mg/150 mg).

A study demonstrated a comparable pharmacokinetic profile following DRV 800 mg co-administered with cobicistat 150 mg once daily<sup>7</sup>, to those of DRV/r 800 mg/100 mg once daily, even if the plasma concentration of DRV is 30% lower when enhanced with COBI. Bioequivalence of DRV administered as a fixed-dose combination with COBI was demonstrated under fasted or fed conditions<sup>8</sup>.

Beyond ART's benefits, regardless of the ARV associated, side effects still significantly influence patients' adherence, increasing the risk of virologic, immunological and tolerability failure. Adverse drug reactions (ADRs), mild or more serious, associated with ART can reverse the gains of therapy, resulting in poor health outcomes. There is a need of an improved understanding of specific ART-related ADRs that influence virologic and immunological response, and also the patients' adherence to the therapy. In a previous study, it was demonstrated that the adverse events during ART are the most important determinants of adherence<sup>9</sup>.

**THE OBJECTIVE OF THE STUDY** was to compare the frequency with which mild side effects occur after administration of a regimen containing DRV boosted with RTV (DRV/r 600 mg/100 mg, twice daily), vs DRV boosted with COBI (DRV/c - 800 mg/150 mg, once a day). The study also performed a profile of a patient at risk of developing all these types of adverse reactions during ARV treatment, by statistically correlating the main self-declared mild side effect with the characteristic parameters for the cohort.

## MATERIALS AND METHOD

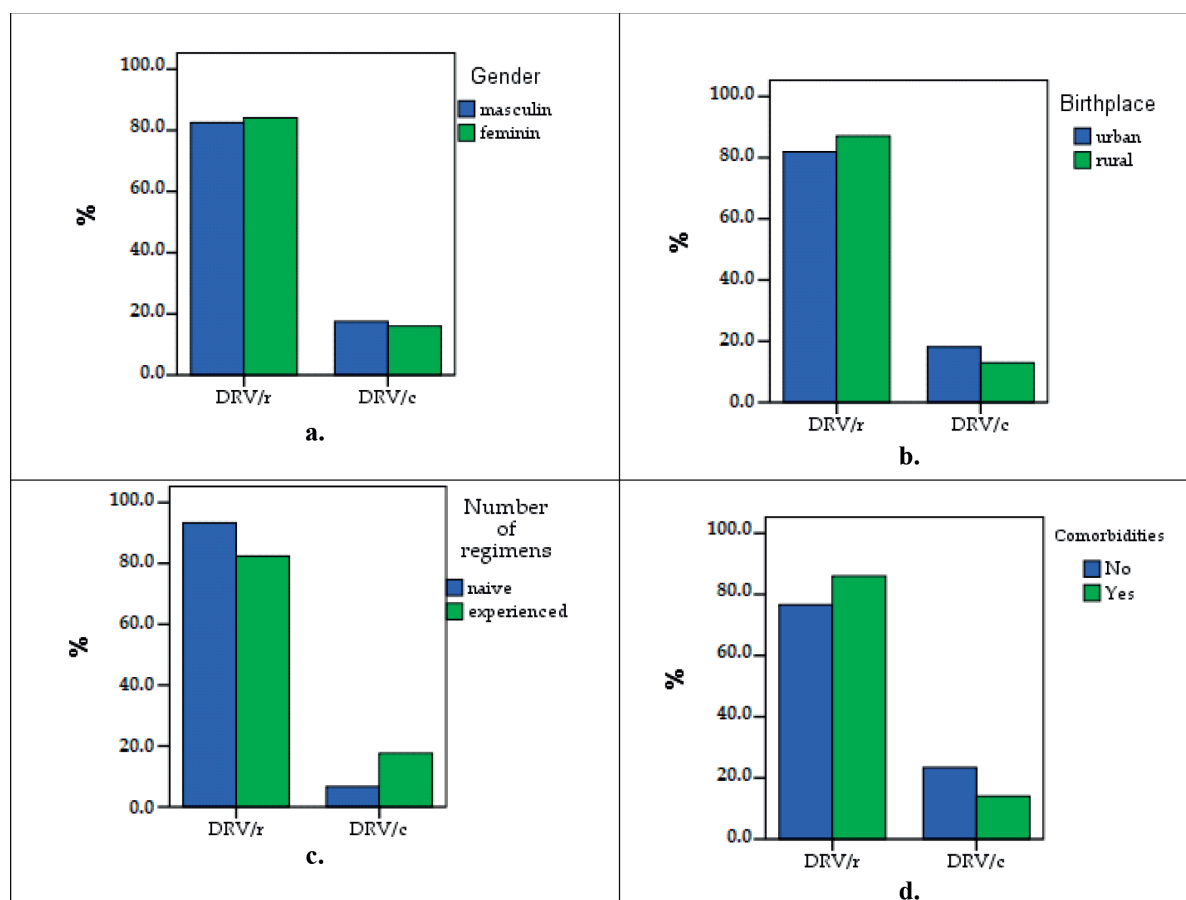
This was a retrospective, non-interventional study, evaluating a cohort of 462 Romanian HIV-infected patients, enrolled in the database of the National Institute of Infectious Diseases “Prof. Dr. Matei Bals”, Bucharest, Romania. The two-arms study has been carried on between October 2017 – December 2020. The cohort was divided into two groups. 384 patients represented the first group and received in the regimen, besides other ARV, DRV boosted with RTV (DRV/r – 600 mg/100 mg, twice daily), while 78 patients, representing the second group, received DRV boosted with COBI (DRV/c – 800 mg/150 mg, once a day). The duration of the treatment, on the last regimen should have been at least three months before the evaluation.

Age over 18 years, ability to discern, the presence in the regimen of the DRV in combination with RTV or COBI, duration of the current therapeutic scheme of at least three months, represented criteria for including patients in the study. The criteria for exclusion were as follows: age under 18 years, clear clinical signs of organ decompensation, lack of discernment, lack of clinical evaluations since the

current therapeutic scheme started, pregnancy and breastfeeding.

Side effects have been encoded according to Medical Dictionary for Regulatory Activities. The adverse events considered to be mild in this study were nausea/vomiting, rash, eczema, sleeping disorders, myalgia, headache, fatigue and hypersensitivity reactions. These reactions were recorded by clinicians during routine medical anamnesis.

The statistical analysis was performed using the SPSS Statistics 20.0.0 program (SPSS Inc., Chicago, IL, USA), for the entire cohort, but also separately for each group. One or more of the following statistical methods have been used: mean, standard deviation, the Pearson correlation coefficient for the quantitative comparison study between two variables; Student’s t Test, expressed by the coefficient  $t$ ; analysis of variance (ANOVA)  $F$ , with statistical significance noted with Sig, to check the influence of qualitative factors, explained by the coefficient  $F$  for three or more independent groups or pairs.  $p < 0.05$  was considered as a significant statistical result. The sign “-” indicates a negative correlation, inversely proportional between the two parameters concerned.



**Figure 1.** Patients' distribution in the two groups according to: a – gender; b – birthplace; c – naive/experienced; d – comorbidities yes/no (SPSS)

The agreements of the Management Commission (9/5861 / 04.05.2021) and Bioethics Commission (C05865/ 04.05.2021) were obtained, for the use of the Institute's database and the waiver of the need for informed consent. The study was conducted in accordance with the ethical principles set out in the Helsinki Declaration and was consistent with the Good Clinical Practice guidelines<sup>10</sup>.

## RESULTS

There were no statistically significant differences in the demographic characteristics between the two assessed groups. Women accounted for 38.50% of the patients of the DRV/r and 35.90% of the DRV/c group. The remaining percentages represented men: 61.50% in the DRV/r group and 64.10% in the DRV/c. Statistically,  $F=0.878$ ,  $t=74.544$  and  $p=0.001$  were obtained. The average age of the patients in the cohort

was 39.27 years (SD 11.32), in the 1<sup>st</sup> group being 39.41 years (SD 11.50) and in the 2<sup>nd</sup> group - 38.57 years (SD 10.45). Considering the birthplace, in the DRV/r group, 75.52% were from urban area, 24.48% from rural area, with 82.05% of urban area and 17.95% of rural areas for DRV/c. Statistically,  $F=7.264$ ,  $t=62.591$ ,  $p=0.001$  were obtained.

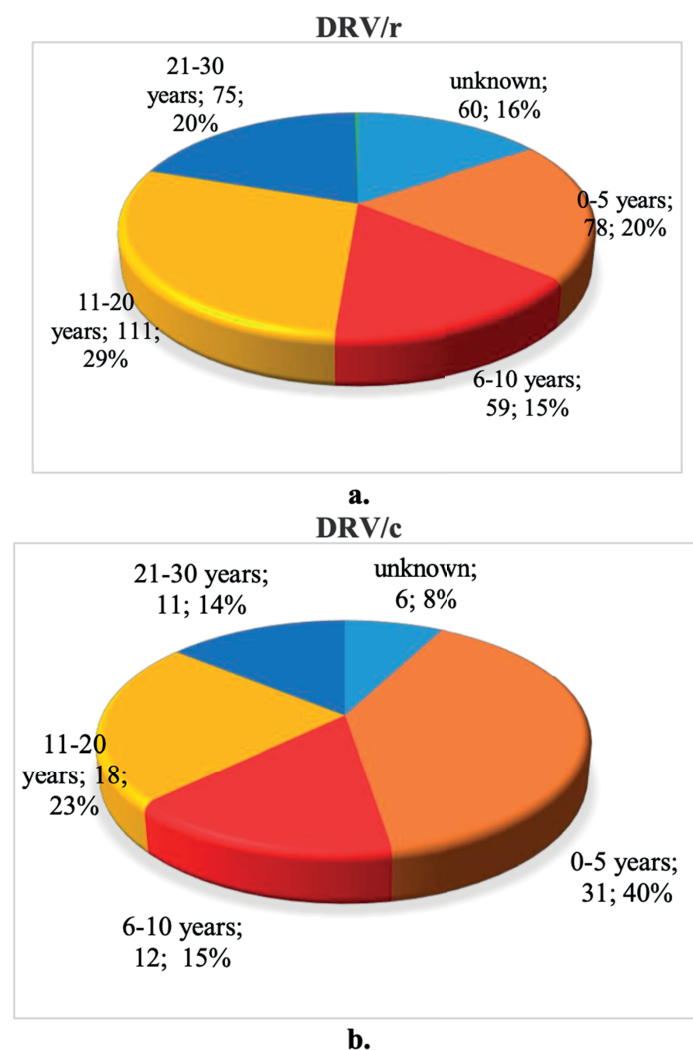
The vast majority of patients in the cohort (93.5%) were therapeutic experienced patients: 92.7% in the DRV/r group and 97.43% in the DRV/c group. Naive patients represented 6.5% in the entire cohort and were distributed as follows: 7.3% in the DRV/r group and 2.56% in the DRV/c group. The description of the patients by gender, birthplace, number of regimens and presence of comorbidities, from the two groups, is presented in Figure 1.

Considering the duration of infection in the group exposed to the DRV/r, the mean value was 11.05 (SD±9.16), in the DRV/c group the mean value was 9.17 (±8.19) and 10.74 (SD±9.02). Statistically, comparing the two groups,  $F=2.792$ ,  $t=25.576$ ,  $p=0.001$  have been obtained (Figure 2).

Considering the duration of ART, for the DRV/r group, the mean value was 11.17 (SD±6.15), for DRV/c 9.57 (SD±6.37), total cohort 10.90 (±6.21). Statistically, comparing the values for the two groups, we obtained  $F=0.003$ ,  $t=37.699$  and  $p=0.001$ . The distribution of patients by duration of ART (years) in the two groups is depicted in Figure 3.

The patients in the two groups were also characterized in terms of the number of regimens experienced since diagnosis. In the entire cohort, the mean value was 8.88 (SD±7.23), for DRV/r group the mean value was 9.09 (SD±7.42) and for DRV/c, the mean value was 7.89 (SD 7.23). In the current regimen, associated with the DRV and the studied enhancers (RTV or COBI), patients received at least one other ARV of a different therapeutic class. The description of the cohort according to HIV therapy, as number and type of therapeutic classes, is presented in Table 1.

The most frequently self-declared mild side effects, following the administration of the current therapeutic regimen, occurred at gastro-intestinal level: nausea/diarrhea were self-declared by 47.10% of the patients in the DRV/r group and by 29.40% in DRV/c group, followed by myalgia (45.80% vs. 12% of the patients in DRV/r group and DRV/c group); fatigue



**Figure 2.** Patients' distribution in the two groups by duration of infection (in years) (Microsoft, Excel)

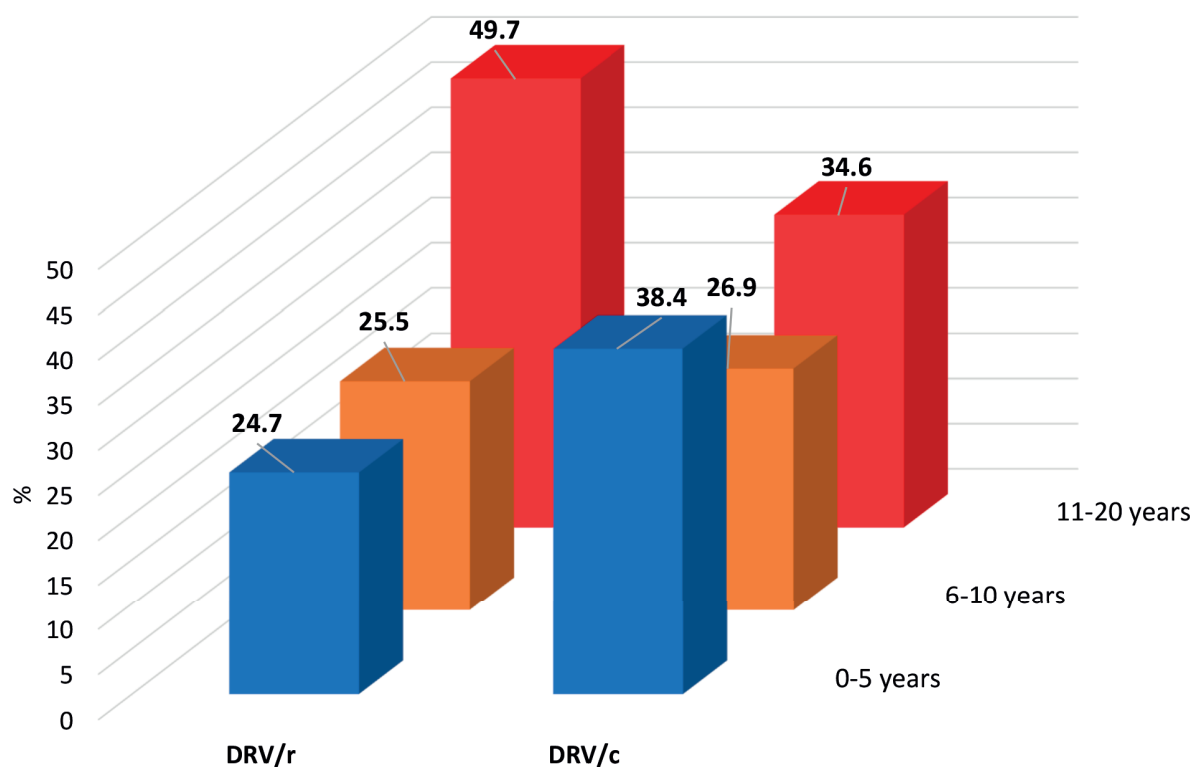


Figure 3. Patients' distribution in the two groups by duration of ART (Microsoft, Excell)

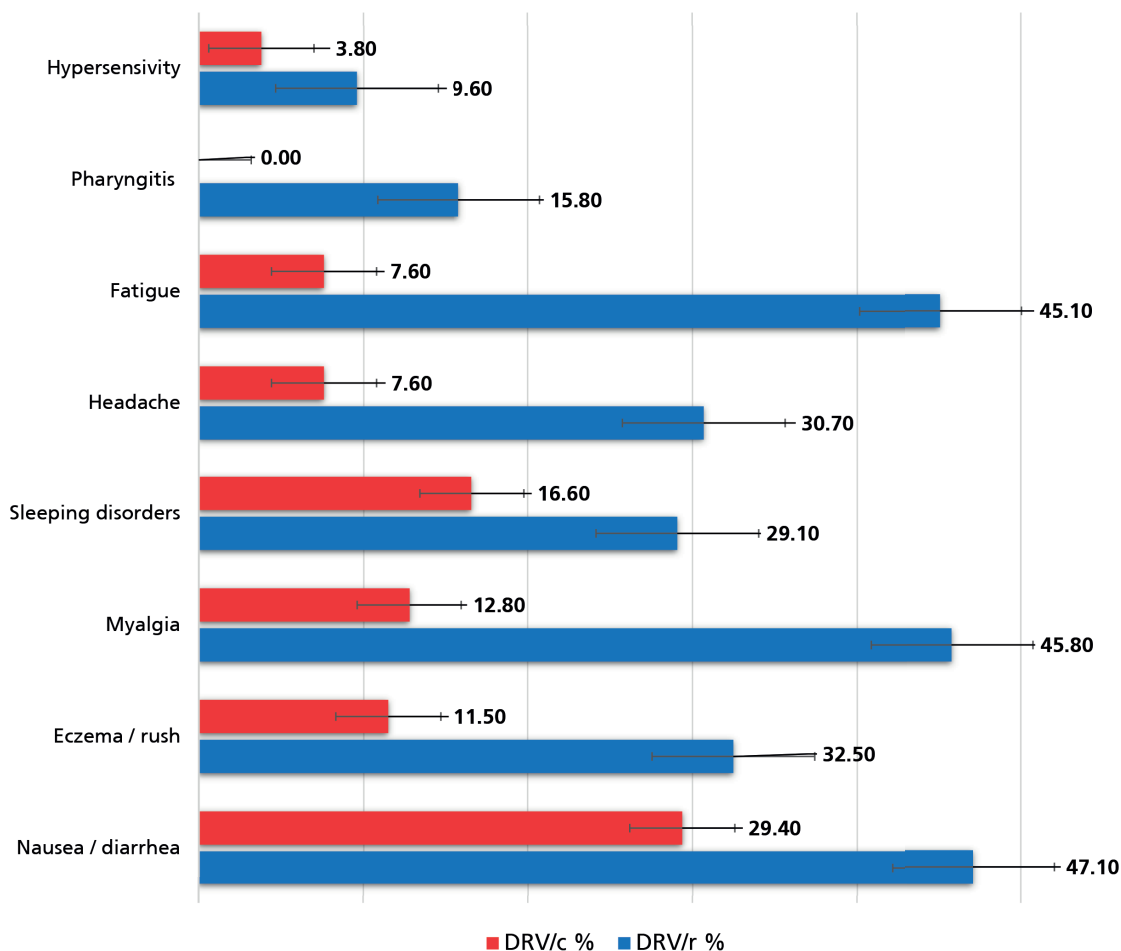
was invoked by 45.10% of patients in the DRV/r group compared to 7.60% in the DRV/c. The most common skin reactions were eczema and rash, most patients with such reactions were in the DRV/r group, 32.50%, compared to 11.50% in the DRV/c group. Hypersensitivity reactions to drug were less frequent, with 9.60% of patients in the first group and 3.80% in the second one reporting the symptom. Headache occurred in 30.70% of patients exposed to the DRV/r vs. only 7.6% of those taking DRV/c. 29.10% of patients in the DRV/r group and 16.60% of the DRV/c group self-declared sleeping disorders occurring during treatment's administration. Pharyngitis was declared only by 15.80% patients in DRV/r group (Figure 4).

Noting with 0 - the absence of symptoms and with 1- their presence, the comparison between the two groups is statistically significant,  $p=0.001$  for all the parameters, as observed in Table 2. Applying independent t Student test and ANOVA variation test, the following results were obtained: nausea/diarrhea  $t=19.092$ ,  $F=66.710$ ,  $Sig.=0.004$ ; eczema/rush  $t=13.724$ ,  $F=109.934$ ,  $Sig.=0.001$ ; myalgia  $t=17.626$ ,  $F=405.383$ ,  $Sig.=0.001$ ; sleeping disorders  $t=13.076$ ,  $F=29.421$ ,  $Sig.=0.023$ ; headache  $t=13.005$ ,  $F=149.032$ ,  $Sig.=0.001$ ; fatigue  $t=17.076$ ,  $F=759.361$ ,  $Sig.=0.001$ ; pharyngitis  $t=8.374$ ,  $F=89.166$ ,  $Sig.=0.001$  and hypersensitivity reactions  $t=6.610$ ,  $F=12.342$ ,  $Sig.=0.098$

Table 1. Therapeutic classes associated with DRV/r or DRV/c presented comparatively for the two groups

Associated ARV classes	DRV/r n=384		DRV/c n=78	
	n	%	n	%
1NNRTI	4	1.04	0	0
1NNRTI+III	22	5.72	0	0
1PI+III	16	4.16	0	0
1NNRTI+IEI	4	1.04	0	0
1NRTI+1NNRTI	22	5.72	0	0
1NRTI+III	23	5.98	4	5.12
1NRTI	6	1.56	0	0
1NRTI+1NNRTI+1PI+III	3	0.78	0	0
2NRTI+1NNRTI	4	1.04	0	0
2NRTI+1NNRTI+III	1	0.26	0	0
2NRTI	252	65.62	70	89.74
2NRTI+III	20	5.20	2	2.56
2NRTI+1PI	1	0.26	0	0
3NRTI+III	1	0.26	0	0
3NRTI+1NNRTI	1	0.26	0	0
3NRTI	1	0.26	0	0
3NRTI+2II	0	0	1	1.28
4NRTI	3	0.78	0	0
4NRTI+III	0	0	1	1.28

Legend: NRTI - nucleoside reverse transcriptase inhibitor, NNRTI - non-nucleoside reverse transcriptase inhibitor, PI - protease inhibitor, II - integrase inhibitor, EI - entry inhibitor, n - number of patients in the group.



**Figure 4.** Distribution of common mild side effects, comparatively in the two groups (Microsoft, Excel)

**Table 2.** Statistical description of the most frequently self-declared mild side effects in the two groups, for  $p=0.001$

Variables	Mean		SD		F	Sig.	t
	DRV/r n=384	DRV/c n=78	DRV/r n=384	DRV/c n=78			
Nausea/Diarrhea	0.5	0.3	0.5	0.5	66.710	0.004	19.092
Eczema/Rush	0.3	0.1	0.5	0.3	109.934	0.001	13.724
Myalgia	0.5	0.1	0.5	0.3	405.383	0.001	17.626
Sleeping disorders	0.3	0.2	0.5	0.4	29.421	0.023	13.076
Headache	0.3	0.1	0.5	0.3	149.032	0.001	13.005
Fatigue	0.5	0.1	0.5	0.3	759.361	0.001	17.076
Pharyngitis	0.2	0.0	0.4	0.0	89.166	0.001	8.374
Hypersensitivity	0.1	0.0	0.3	0.2	12.342	0.098	6.610

(Table 2). The graphical representation of the mean values of the most frequently self-declared mild side effects can be seen comparatively between the two groups in Figure 5.

In order to determine the profile of the patient at risk of developing mild side effects studied, at ARV administration, cohort demographic parameters were correlated with the frequency of mild side effects.

The study obtained the following results, with statistical significance:

- myalgia correlates strongly positively ( $p<0.01$ ), directly proportional to the patients' age,
- sleeping disorders and age correlate strongly positively ( $p<0.01$ ),
- fatigue relates strongly positively ( $p<0.01$ ) to age, to number of ARV regimens and with a

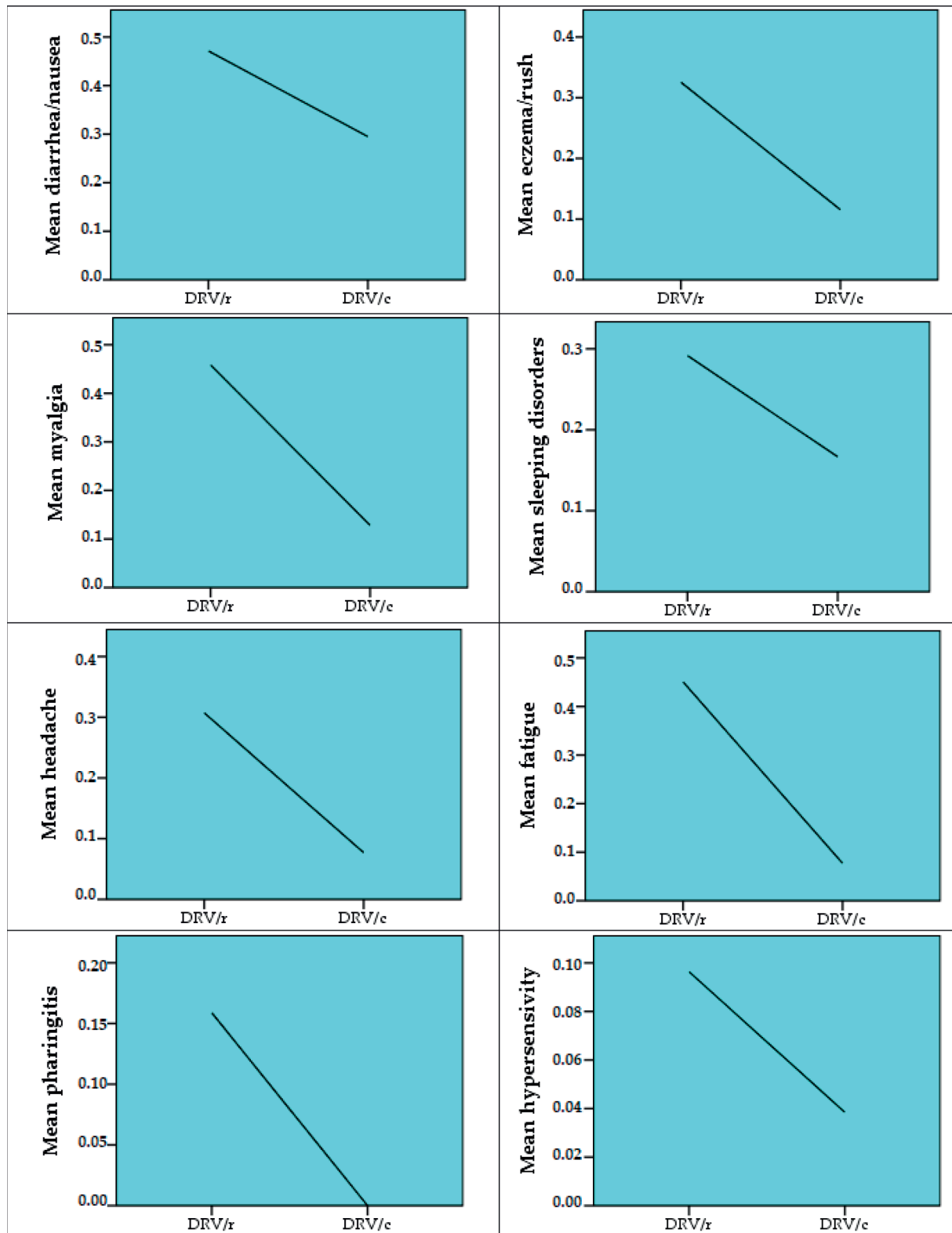


Figure 5. The mean values of the most frequently self-declared mild side effects comparing the two groups (SPSS)



**Table 3.** Pearson correlation between the risk of mild side effects and demographic parameters in the cohort

Variables	Nausea/ diarrhea	Eczema/rush	Myalgia	Sleeping disorders	Headache	Fatigue	Pharyngitis	Hypersensitivity
Age	0.084 (p=0.073)	-0.001 (p=0.982)	0.326** (p=0.001)	0.206** (p=0.001)	0.075 (p=0.106)	0.163** (p=0.001)	0.084 (p=0.071)	0.025 (p=0.585)
Duration of ART	0.012 (p=0.789)	-0.003 (p=0.946)	-0.019 (p=0.690)	0.022 (p=0.632)	0.001 (p=0.984)	0.033 (p=0.484)	-0.036 (p=0.441)	0.003 (p=0.952)
Number of ARV regimens	0.046 (p=0.319)	0.034 (p=0.462)	0.003 (p=0.950)	0.040 (p=0.394)	0.041 (p=0.379)	0.127** (p=0.006)	0.036 (p=0.440)	-0.028 (p=0.548)
Number of comorbidities	-0.013 (p=0.775)	-0.044 (p=0.340)	0.019 (p=0.679)	-0.037 (p=0.425)	0.080 (p=0.085)	-0.079 (p=0.090)	-0.001 (p=0.983)	0.019 (p=0.689)
Pill' s burden	0.056 (p=0.229)	-0.037 (p=0.442)	0.017 (p=0.709)	0.032 (p=0.493)	-0.028 (p=0.543)	0.110* (p=0.018)	-0.009 (p=0.842)	-0.024 (p=0.607)

p - statistical significance, \* - statistical significance  $p < 0.05$ , \*\* - statistical significance  $p < 0.01$ , „-“, indicates a negative correlation, inversely proportional between the two parameters concerned.

statistical significance of  $p < 0.05$  with the pills burden (Table 3).

The other parameters do not reach the threshold of statistical significance when correlating to the demographic characteristics of the patient cohort.

## DISCUSSION

Simplified treatment regimens, with as little pill burden as possible, few side effects and maximum efficacy represent the goals in the management of antiretroviral therapy.

This study revealed a number of self-declared mild side effects after administration of ARV, which are not related to changes in serum or metabolic markers, but they depend on the perception of each patient: nausea/diarrhea, eczema/rush, myalgia, sleeping disorder, headache, fatigue, pharyngitis, or hypersensitivity reaction. For clinicians, the challenge is to manage patients' attitude toward these reactions, most of which disappearing after a few weeks of administration. The long-term persistence of these reactions may compromise the success of therapy, by losing patients' adherence to treatment. The study results have shown that virologic and immunological response to therapy remains favorable in most patients. It is difficult to say, however, whether or what percentage of patients in therapeutic failure (HIV-1 RNA load  $> 1000$  copies/mL and/or CD4 lymphocytes  $< 0-199$  cells/mm<sup>3</sup>) is caused by discontinued therapy. At the clinical anamnesis, an extremely high percentage of patients (on average of 91.5%) declared that they had taken the treatment according to the dosage prescribed.

Long before the outbreak of the HIV/AIDS epidemic, sociologists described how everyone's perceptions of the disease and of different symptoms influences their attitude and behavior toward treatment<sup>11</sup>.

Regarding ART, fear or a previous bad experience with a drug, for example side effects on zidovudine, have been shown to lead to decreased adherence<sup>12</sup>. Data from another study confirm that the perception of adverse symptoms developed in the first four months of a regimen is a critical determinant of adherence. The way a patient relates to drugs' side effects, whether or not related to the toxicity of the drug, is a good indicator of patients' difficulties in managing the daily life course of the treatment<sup>13</sup>.

It is not possible to establish precisely if the self-declared reactions were caused by the ARV. However, the present study has shown that all the symptoms occur with a higher incidence in the regimen containing RTV than with COBI as pharmacokinetic enhancer. The differences have statistical significance,  $p < 0.01$  for all parameters. This underlines that the patients exposed to DRV/c have a better tolerability profile than those taking DRV/r, thus leading to a greater adherence to treatment. Previous studies that have evaluated the tolerability profile of RTV confirm the results of this study<sup>14</sup>.

Gastrointestinal reactions, nausea and vomiting were present in 47.2% of patients in the DRV/r group and in 29.5% of the subjects in the DRV/c group. Both the ART, in particular protease inhibitor regimens<sup>15</sup>, and various opportunistic infections with protozoa, fungi, viruses and bacteria are responsible for these symptoms.

Still, the nature of HIV-related diarrhea has shifted from being predominantly a consequence of opportunistic infection to being largely a side effect of ART agents. Previous studies have shown that a quarter of HIV<sup>+</sup> patients present diarrhea, that has a negative impact on their life quality<sup>16</sup>. The negative effect on quality of life in patients with ART-related diarrhea is profound; diarrhea may also increase the risk of poor adherence to treatment, with potentially

serious effects on viral suppression and increased risk of drug resistance<sup>17</sup>.

However, in a study carried out on a cohort of patients in Italy, in whom both PI and NRTI were administered, it was shown that diarrhea does not decrease immediately the patient adherence, although this type of reaction is extremely frequent among patients and does not disappear after the first weeks of administration<sup>13</sup>. PI is also responsible for the appearance of nausea, and RTV is well-known to have this side effect, with 20% of patients accusing it after RTV administration<sup>14</sup>.

Patients in this study have self-declared the occurrence of rash and eczema. 32.55% (DRV/r) compared to 11.53% (DRV/c) patients accused these symptoms. The average of the values for the first group is 0.32 (SD±0,46) compared to an average of 0.11 (±SD 0.32) for the second group. The comparative results obtained when carrying out the t Student and ANOVA tests, the F coefficients are statistically relevant ( $p < 0.05$ ), with a high risk of occurrence in the DRV/r group and thus lower safety for those exposed to the RTV. The results of this study are consistent with those demonstrated by other studies. In 2014, the study carried out by Nishijima and colleagues pointed out that these skin reactions occur frequently when taking DRV, especially when it is enhanced with RTV. However, most patients can get over these symptoms when associating an oral antihistamine or corticosteroid treatment<sup>18</sup>.

Before this study, data on the prognosis and incidence of skin rashes and eczema after ARV administration were limited. The only information came from the summary of product characteristics (SMPC)<sup>19,20</sup>. More recently, DRV has been reported to cause rash in 6.7% of patients, with severe symptoms in less than 1% of them, especially when boosted with RTV<sup>21</sup>. According to the same SMPCs, myalgia is a side effect that can occur very frequently in patients exposed to RTV and frequently when administering COBI<sup>20,22</sup>.

Our study recorded the occurrence of these reactions in 45.9% of patients who received DRV/r and in only 12.9% of those in the second group, DRV/c. Comparing the two groups, the results have statistical significance, the mean value for the first group is 0.45, while for the second is 0.33. Although the risk of these symptoms is present for both regimens, the incidence is much higher in subjects in DRV/r group. Although frequently self-declared by patients, no targeted studies have been carried out on this subject. Fatigue and sleep disorders go hand in hand, often declared by patients under ARV treatment<sup>23,24</sup>. In our study, 45.1% of patients in the group exposed to the DRV/r and only 7.7% of those exposed to the DRV/c

complained of chronic fatigue during treatment. The statistical difference between the two groups is extremely high, with  $F=759.361$  and  $t=17.076$ , significance  $p < 0.001$ . Sleep disorders were present in 29.2% of the subjects from the DRV/r group and 16.7% in the DRV/c group.

A study carried out among HIV-positive teenagers showed that chronic fatigue is perceived as problematic, having a considerable impact on their daily lives, affecting their ability to concentrate at school or socialize with their peers<sup>25</sup>. However, in order to be able to demonstrate the link between ART and sleeping disorders, further studies are required to compare a cohort exposed to ART with one not exposed. In the first group, (DRV/r) 30.72% self-declared headaches as mild symptom, while in the second group (DRV/c) only 7.69% of subjects recalled its presence during treatment. The statistical difference is important, the significance being  $p < 0.001$ , with ANOVA coefficient  $F=149.032$  and t Student test coefficient,  $t=13.005$ .

Headache is one of the most common complaints in this patient cohort. Some previous studies have found a correlation between the HIV infection itself and primary headache disorders, others demonstrated more of a link to secondary causes, caused by opportunistic infections often associated with HIV. All patients in these studies were taking ART<sup>26,27</sup>.

However, data are lacking regarding the prevalence and diagnostic characteristics of headache among HIV patients in the current ART era. Studies have obtained divergent findings regarding the prevalence of headache disorders among HIV patients, all of them being conducted before the wide spread proliferation of ART<sup>28</sup>.

The only patients who mentioned pharyngitis (during ARV's administration) were those in the group exposed to RTV, 15.88%. The difference between groups is statistically significant, with a mean value of 0.15 vs. 0.00,  $t=8.374$  and  $F=14.667$ . In addition, the SMPC mentions that side effects such as pharyngitis, coughing or oropharyngeal pain may occur very frequently with the long term RTV administration<sup>20</sup>. We did not find any previous studies that had investigated the prevalence of this symptom among HIV<sup>+</sup> patients.

Hypersensitivity reactions to therapy occurred with a rate of less than 10% across the cohort, but with a significant difference between the two groups, 9.63% (DRV/r) versus 3.84% (DRV/c). Both results are in line with the frequency stipulated in the SMPCs<sup>20,22</sup>. Comparing the two groups, the results have statistical significance,  $p < 0.001$ ,  $t=6.610$  and  $F=12.342$ . Previous studies have shown that hypersensitivity reactions and allergies occur 100 times more

frequently in people infected with HIV than in the general population<sup>29</sup>. Many ARV or drugs used for the opportunistic infections can cause drug hypersensitivity reactions, which vary in severity, clinical manifestations and frequency. These reactions are not only seen with the older ones, but also with the newer molecules recently introduced in therapy. The most frequently incriminated therapeutic classes are NNRTI and PI. Abacavir causes hypersensitivity reaction in 2-4% of patients, reactions that can even have a lethal end<sup>30</sup>.

The current study also performed a patient profile with a risk of developing all these types of adverse reactions during ARV treatment. We have statistically correlated the main self-declared mild side effect with the characteristic parameters for the cohort. The results showed that myalgia and sleep disorders have a higher risk of occurring in patients with a higher pill's burden. The heavier the pill's burden, the more often they occur. Chronic fatigue correlates strongly positively ( $p < 0.01$ ) directly proportional to the pill burden. The more pills a patient takes once, the greater the risk of fatigue. Fatigue is also positively correlated ( $p < 0.05$ ) with the number of comorbidities. The more diseases a HIV-infected patient suffers from, the more often fatigue occurs.

## CONCLUSIONS

ART regimens containing DRV/c appear to have a higher tolerability than those containing DRV/r. This was statistically proven in the present study by frequency of mild side effects, which are less often self-declared by patients who have received DRV/c. Patient adherence depends on the frequency and intensity of side effects. The results of our study strongly emphasize that management of mild side effects should be an important part of the antiretroviral therapy, in order to promote adherence.

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Conceptualization, R.C.M.; methodology, R.C.M. and S.B.; software, R.C.M.; validation, S.B.; formal analysis, R.C.M.; investigation, R.C.M.; resources, R.C.M.; data curation, R.C.M.; writing—original draft preparation, R.C.M. and S.B.; writing—review and editing, R.C.M., and S.B.; visualization, A.S.C. and S.B.; supervision, A.S.C. and S.B.; project administration, S.B. All authors have read and agreed with the final version of this article.

## Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article”

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study”

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