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RESEARCH ARTICLE

Real World Patient-reported Outcomes in HIV-infected Adults Switching to EVIPLERA®, Because of a Previous Intolerance to cART. PRO-STR Study

D. Podzamczer[1,*], N. Rozas[1], P. Domingo[2], C. Miralles[3], E. Van den Eynde[1], A. Romero[4], E. Deig[5], H. Knobel[6], J. Pasquau[7], A. Antela[8], B. Clotet[9], P. Geijo[10], E. Rodríguez de Castro[11], M.A. Casado[12], A. Muñoz[12], A. Casado[12] for the PRO-STR Study Group

[1]Hospital Universitari de Bellvitge, Barcelona, Spain; [2]Hospital de la Santa Creu y Sant Pau, Barcelona, Spain; [3]Hospital Xeral de Vigo, Pontevedra, Spain; [4]Hospital de Especialidades de Puerto Real, Cadiz, Spain; [5]Hospital General de Granollers, Barcelona, Spain; [6]Hospital del Mar, Barcelona, Spain; [7]Hospital Universitario Virgen de las Nieves, Granada, Spain; [8]Complejo Hospitalario Universitario de Santiago, A Coruña, Spain; [9]Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; [10]Hospital Virgen de la Luz, Cuenca, Spain; [11]Hospital Mateu Orfila, Mahon, Spain; [12]Pharmacoeconomics & Outcomes Research Iberia, Madrid, Spain

Abstract: ***Background*:** To investigate the impact of switching from stable Combined Antiretroviral Therapy (cART) to single-tablet regimen (RPV/FTC/TDF=EVIPLERA®/COMPLERA®) on patient-reported outcomes in HIV-infected adults who cannot tolerate previous cART, in a real-world setting.

***Methods*:** PRO-STR is a 48-week observational, prospective, multicenter study. Presence and magnitude of symptoms (main endpoint), health-related quality-of-life (HRQoL), adherence, satisfaction with treatment and patient preferences were assessed.

***Results*:** Three hundred patients with 48-week follow-up, who switched to EVIPLERA® (mean age: 46.6 years; male: 74.0%; 74.7% switched from a non-nucleoside reverse-transcriptase-inhibitor, 25.3% from a protease inhibitor + ritonavir) were included. There was no statistical difference in median CD4+ cell count (baseline: 678.5 cells/mm^3; 48-week: 683.0 cells/mm^3) neither in virological suppression (≤50 copies/mL) (baseline: 98.3%; 48-week: 95.3%). The most frequent reasons for switching were neuropsychiatric (62.3%), gastrointestinal (19.3%) and biochemical/metabolic (19.3%) events. Only 7.7% of patients permanently discontinued therapy. At 48-week, all outcomes showed an improvement compared to baseline. Overall, there was a significant decrease (p-value≤0.05) in number and magnitude of symptoms, while HRQoL, satisfaction and adherence improved significantly. Most patients prefered EVIPLERA® than previous cART. According to the type of intolerance, HRQoL was improved, but only significantly in patients with neuropsychiatric and gastrointestinal symptoms. Adherence improved significantly in patients with metabolic disturbances and satisfaction with EVIPLERA® was higher in the three groups.

***Conclusion*:** Switching to EVIPLERA® from non-nucleoside reverse-transcriptase-inhibitor or protease inhibitor-based regimens due to toxicity, improved the presence/magnitude of symptoms, HRQoL, and preference with treatment. EVIPLERA® maintained a virological response, CD4+ cell count and maintained or improved adherence.

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1. INTRODUCTION

The use of highly active antiretroviral therapy (HAART) has changed the outcome and management of patients infected with human immunodeficiency virus (HIV). Long term viral suppression and restoration of CD4+ lymphocytes level have improved health outcomes and prolonged life expectancy of infected patients, transforming HIV infection into a chronic disease [1, 2].

However, several ART regimens have still important limitations such as adverse events, number of pills, and drug-drug interactions, negatively influencing health quality and adherence, and subsequently, making difficult the long term success of treatment.

*Address correspondence to this author at the HIV and STD Unit. Infectious Disease Service, Hospital Universitari de Bellvitge. L'Hospitalet del Llobregat. 08907. Barcelona. Spain; Tel: 34-932 607 667 / 34-630 268 621; Fax: 34-932607669; E-mail: dpodzamczer@bellvitgehospital.cat

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Single-tablet regimens (STRs) are an important advance in the management of HIV infection. These regimens involve only one pill administered once a day and their use has been associated with an improvement in treatment adherence, a reduction in the rate of hospitalization, greater therapeutic success rates, and reductions in mortality [3-5].

For this reason, Patient-Reported Outcomes (PRO), and particularly, health-related quality-of-life (HRQoL), are important in health outcome research to measure the potential repercussions in the quality-of-life of HIV infected patients [6-8].

The review of recent studies suggests a lack of consensus concerning the optimal instruments for the measurement of PRO [9], in addition to the need for more pragmatic approaches that collect data regarding the administration of medications in the real-world setting [10]. Any information communicated directly by patients about their health condition and treatment, including symptoms, functional state, satisfaction with treatment, preference, and adherence to treatment, is essential in the health decision-making process [10].

The objective of this study was to investigate the impact of switching from a non-nucleoside reverse transcriptase inhibitor (NNRTI)– or a protease inhibitor (PI)-based cART regimen to the STR regimen [rilpivirine (RPV)/emtricitabine (FTC)/tenofovir (TDF): EVIPLERA®/COMPLERA®] because of therapy intolerance, on patient-reported outcomes, in routine clinical practice.

2. METHODS

The PRO-STR is a multicenter, observational, open-label, non-randomized, single arm, post-authorization prospective follow-up study of routine clinical practice. The study was evaluated and approved by the Institutional Review Boards of the participating centers and was conducted in accordance with the Helsinki Declaration. In order to adjust to the follow up that is done in Real World, the study consisted of 5 visits: the baseline visit (change from cART to EVIPLERA®) and visits on week 4, week 16, week 32 and week 48. In this analysis, the results obtained up to the week 48 visit are described. Of all the patients who completed the baseline visit and the week 4 visit, some were excluded at the beginning of the week 16 visit for various reasons: missing values for the main variables, not having completed the corresponding follow-up visits and discontinuation of treatment (Fig. **1**).

Adult patients, HIV-infected, who had a viral load less than1,000 copies/mL, who required switch to STR (EVIPLERA®) due to a intolerance to previous treatment with cART (combination of at least three drugs that included two nucleoside analogs and a protease inhibitor boosted with ritonavir [PI/r] or a nucleoside non-analogue; or 2 nucleoside analogues+ 1 integrase inhibitor) were identified. Eligibility criteria included the duration of previous cART for at least 12 months, and maintenance without changes to the regimen and the dosage of the previous cART for at least the previous 3 months. Patients also had to have signed an informed consent form. Intolerance was defined as any adverse event with a grade 2 to 4 laboratory anomaly (according to the WHO scale [11]) that induced a switch to the EVIPLERA®. Intolerances were classified by the symptoms indicated by the patients and by the results of the laboratory tests into the following groups: neuropsychiatric (sleep disorders and alterations in mood), gastrointestinal (nausea, vomiting, or diarrhea) and metabolic (hypercholesterolemia, hypertriglyceridemia, anemia, and alterations in carbohydrate metabolism).

Sociodemographic data were collected from the patients (age, gender, level of education, and work status), as were clinical disease data (co-infections, viral load, and CD4+cell count), intolerances, treatment discontinuations, and PRO, through a series of questionnaires that were auto administered in all visits, to be fulfilled by the included patients.

In total, 5 questionnaires were collected: the ACTG (AIDS Clinical Trials Group)-HIV Symptom Index [12], EQ-5D (EuroQol-5D) [13-15], MOS-HIV (Medical Outcomes Study HIV Health Survey) [16, 17], SMAQ (Simplified Medication Adherence Questionnaire) [18], ESTAR (Escala de Satisfacción con el Tratamiento Antiretroviral) [19, 20], besides of a question related to the SRT patient-preference.

The main endpoint of the study was the reduction in the number and severity of symptoms at 48 weeks using the ACTG symptom index [21]. The ACTG indicates the presence of symptoms, with a range of 0 to 20 symptoms, and the degree of discomfort caused by the symptoms, with a range of 0 (no discomfort) to 80 (much discomfort). The HRQoL was evaluated using the EQ-5D and MOS-HIV questionnaires. The EQ-5D measures the general state of health. The EQ-5D score range from 0 (death) to 1 (best possible health state); negative values correspond to those health states that are scored as worse than death. In addition, the EQ-5D includes a visual analogue scale (VAS) in the form of a thermometer with a scale from 0 (worst health state imaginable) to 100 (best health state imaginable). The MOS-HIV is an HRQoL-specific questionnaire that evaluates 11 dimensions with scores that transform to a scale that ranges between 0 (worst quality of life) and 100 (best quality of life). From these scores, two components were calculated: physical and mental. These components have a mean of 50 and a standard deviation of 10. If the scores obtained were close to 50, the patients were said to have an HRQoL that did not significantly differ with respect to the reference population (the population with HIV infection). However, if the scores obtained differed from 50 by more than 10 points (less than 40 or more than 60), patients were said to have an HRQoL that was significantly better or worse than the reference population. Adherence to STR was evaluated with the SMAQ questionnaire, which comprised six questions. A patient is considered non-adherent, when at least one answer is "yes" to questions 1 (Do you ever forget to take the medication?), 3 (Do you ever stop taking the drugs if you feel sick?) and 4 (Did you forget to take the medication during the weekend?) or answer "no" to question 2 (Do you always take your medication at the indicated time?). In question 5 (In the last week, how many times did you not take any dose?) to answer more than 2 doses lost in the last week, it is considered non-adherent. In question 6 (In the past three months, how many full days did you not take the medication?) to answer that in

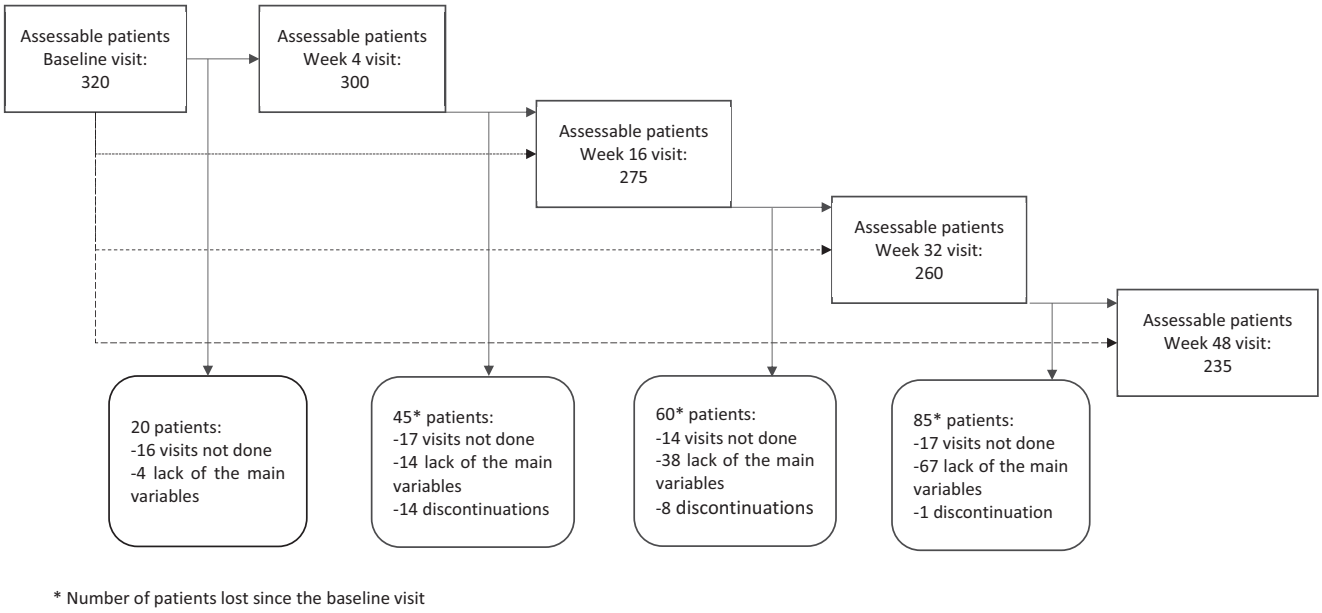

Fig. (1). Patients follow up flow chart.

the last 3 months, there have been more than two days that treatment has not been administered, it is considered non-adherent. Satisfaction with EVIPLERA® was evaluated using three questions on the ESTAR, which references convenience, flexibility, and ease of use of the treatment, with scores that range between 0 (not at all satisfied) and 6 points (very satisfied). Finally, to measure patient's STR preference, the following question was asked with five possible response options (much worse to much better): "How is the patient doing with the current ART compared with the ART that his/her doctor had previously prescribed for his/her HIV infection?".

The PRO results were separately presented in three subgroups as a function of the intolerance to treatments administered prior to the baseline visit: patients with gastrointestinal, neuropsychiatric, and metabolic intolerances, in order to test the influence over the results of the type of previous intolerance. Patients could exhibit more than one type of intolerance; thus, there exist patients who belong to more than one subgroup. In case of missing data for a patient that did not allow estimate the overall score in a questionnaire, the information of this patient was excluded for the aforementioned questionnaire. The progression of PROs was obtained by comparing results from the baseline visit with those from the week 48 visit.

To determine the sample size, the results of ACTG-HIV Symptom Index in the study of Hodder were considered [22]. At the beginning of that study, the percentage of patients with diarrhea and other intestinal problems was 44%. This percentage was reduced to 33% at the end of the study. With these results, 511 patients were needed to find a statistically significant difference with an alpha risk of 0.05, a power of 0.90 and a loss to follow up of 25%. The sample size calculation was performed using GRANMO version 7.10. The statistical analysis was performed using the R statistical program, version 2.13.0. An α risk value equal to 0.05 was assumed (significant difference: p-value$\leq$0.05). For continuous variables, means and standard deviations were reported; the One-way ANOVA with repeated measures was used. For categorical variables, frequencies and percentages were computed; the Pearson Chi-squared or the McNemar tests were used according to the type of variable evaluated. Statistical contrasts were also computed for prospective individual comparisons. In cases that did not satisfy the assumptions of these parametric tests, the equivalent non-parametrical tests were used.

3. RESULTS

3.1. Baseline Characteristics and Changes in Virologic and Immunological Parameters

A total of 300 patients belonging to 25 centers (APPENDIX I – PRO-STR STUDY GROUP) who changed their previous treatment to EVIPLERA® and completed the baseline visit and the corresponding 4-week visit, were included in the analysis; 275 completed the week 16 visit; 260 completed the week 32 visit and 235 completed the week 48 visit (Fig. **1**). There were 85 missing patients between the baseline visit and the week 48 visit due to several reasons such as: visits not done (17 patients), lack of the main variables (67 patients) and discontinuations (1 patient).

Patients with and without loss of follow-up are basally comparable among themselves because no statistically significant differences were found between both groups of patients in basal scores (except in education level) (data not shown).

Although a conservative approach to estimate the sample size was adopted (511 patients), finally 300 patients were included since many of them either did not accept to participate or did not meet the criteria required in the study.

Sociodemographic characteristics are presented in Table **1**. The previous cART in 74.7% of patients was a NNRTI-based regimen [67.0% efavirenz (EFV) of the total number

of patients] and in 25.3% a PI/r-based regimen [10.7% FTC/TDF + darunavir boosted with ritonavir (DRV/r)]; 8.0% FTC/TDF + atazanavir boosted with ritonavir (ATV/r); and 5.3% TVD + lopinavir boosted with ritonavir (LPV/r)]. Twenty-three (7.7%) patients discontinued treatment definitively as a result of the following: adverse events (2 patients, 0.7%), lack of efficacy (2 patients, 0.7%) tolerance problems (6 patients, 2.0%), and/or for other reasons (14 patients, 4.7%). Patients could have more than one reason why discontinuation occurred.

Table 1. Baseline characteristics of the subjects included (n=300).

Male **gender**, n (%)	222 (74.0%)
Age, mean (median, IQR*)	46.56 (47.00, 13.00)
Education level, n (%)	
Elementary or less	121 (40.3%)
Secondary	102 (34.0%)
University	77 (25.7%)
Employment status, n (%)	
Self-employed/Salaried	194 (64.7%)
Housewife	14 (4.7%)
Unemployed	51 (17.0%)
Pensioner / Disability	37 (12.3%)
Other	3 (1.0%)
No data	1 (0.3%)
Hepatitis B coinfection, n (%)	12 (4.0%)
Hepatitis C coinfection, n (%)	41 (13.7%)
Years since HIV diagnosis, mean (median, IQR)	12.72 (11.00, 11.00)
Years on ART, mean (median, IQR)	8.28 (6.77, 8.77)
Years on last ART, mean (median, IQR)	4.06 (4.05, 3.42)
Number of previous ART regimens, mean (median, IQR)	2.55 (2.00, 2.00)
Type of intolerance* to previous ART, n (%)	
Gastrointestinal	58 (19.3%)
Central nervous system-psychiatry	187 (62.3%)
Metabolic	58 (19.3%)
Others	29 (9.7%)
Previous ART components, n (%)	
NNRTI	224 (74.7%)
Efavirenz [EFV]	201 (67.0%)
Nevirapine [NVP]	13 (4.3%)
Etravirine [ETR]	10 (3.3%)
PI/r	76 (25.3%)
Darunavir/r [DRV]	32 (10.7%)
Atazanavir/r [ATV]	24 (8.0%)
Lopinavir/r [LPV]	16 (5.3%)
Fosamprenavir/r [FPV]	2 (0.7%)
Lopinavir [LPV]	1 (0.3%)
Fosamprenavir [FPV]	1 (0.3%)
Ritonavir [RTV]**	74 (24.7%)

IQR: Interquartile range; ART: antiretroviral therapy
*Patients could exhibit more than one type of intolerance
** Patients with ritonavir as PI booster

An undetectable viral load (≤50 copies/mL) was maintained in the majority of patients (baseline visit: 98.3%; week 48 visit: 95.3%; p-value>0.05). There were only 10 patients with undetectable viral load in the baseline visit who had an increase at the week 48 visit (between 50 copies and 1.000 copies/mL), because of not being adherent to their treatment with Eviplera.

The CD4+ count did not significantly vary throughout the visits (baseline visit: 678.5 cells/mm3; week 48 visit: 683.0 cells/mm3; p-value>0.05). However, the proportion of patients with a CD4+ count greater than 500 cells/mm3 significantly increased in week 48 (baseline visit: 73.0%; week 48 visit: 76.4%; p-value≤0.05).

3.2. PRO Results in the Overall Population

The results of the ACTG, EQ-5D, and MOS-HIV questionnaires are presented in Table **2**. In the ACTG questionnaire, a statistically significant decrease was observed (p-value≤0.05) in the number of symptoms and degree of discomfort of these symptoms at week 48 visit compared with the baseline visit in all patients.

In the EQ-5D questionnaire, a statistically significant improvement in the health status was observed (p-value≤0.05).

The results of the physical and mental components of the MOS-HIV questionnaire indicate that, at week 48 visit, patients did not exhibit any significant differences compared with HIV-infected patients and blood donors, the reference populations with whom this test was validated because the scores are close to 50. In addition, a statistically significant improvement (p-value≤0.05) versus the baseline visit was observed in the physical and mental component.

Table **3** includes the treatment adherence results estimated using the SMAQ questionnaire. Adherence to treatment was statistically significant improved (p-value≤0.05).

Satisfaction with the new treatment (EVIPLERA®), measured through the ESTAR questionnaire, is presented in Table **3**. All patients reported greater satisfaction with the ease, the convenience and with the flexibility of use of the new treatment compared with the old treatment (p-value≤0.05).

Table 2. Health-related quality of life (ACTG, EQ-5D-3L and MOS-HIV) according to previous intolerance (gastrointestinal, neuropsychiatric or metabolic).

	Baseline	Week 4			Week 48		
	Mean±SD* (n)	Mean±SD* (n)	Difference (vs Baseline)	p-Value	Mean±SD* (n)	Difference (vs Baseline)	p-Value
ACTG Symptom Index: number of symptoms (0: best; 20: worst)							
Total	9.6±5.6 (287)	7.1±6.0 (286)	-2.45	**<0.001**	6.8±6.5 (227)	-2.76	**<0.001**
Gastrointestinal	10.5±6.2 (51)	7.9±6.5 (54)	-2.58	**0.001**	7.8±7.6 (47)	-2.65	**0.001**
Neuropsychiatric	10.2±5.3 (182)	7.2±6.0 (178)	-3.06	**<0.001**	6.8±6.6 (142)	-3.37	**<0.001**
Metabolic	7.3±5.6 (55)	6.4±12.6 (56)	-0.89	0.148	5.0±5.1 (41)	-2.25	0.116
ACTG Symptom Index: degree of discomfort (0: best; 80: worst)							
Total	20.3±14.0 (287)	12.5±12.2 (286)	-7.83	**<0.001**	11.3±12.4 (227)	-8.96	**<0.001**
Gastrointestinal	22.5±15.0 (51)	12.6±10.6 (54)	-9.94	**<0.001**	12.1±13.4 (47)	-10.42	**<0.001**
Neuropsychiatric	21.7±13.8 (182)	12.7±12.3 (178)	-8.96	**<0.001**	11.4±12.7 (142)	-10.28	**<0.001**
Metabolic	14.8±12.6 (55)	11.1±12.2 (56)	-3.77	**0.005**	8.3±9.4 (41)	-6.48	**0.003**
EQ-5D Index Score (0: worst; 1: best)							
Total	0.82±0.18 (300)	0.88±0.16 (298)	0.06	**<0.001**	0.90±0.16 (232)	0.08	**<0.001**
Gastrointestinal	0.81±0.19 (58)	0.89±0.14 (57)	0.08	**<0.001**	0.90±0.17 (48)	0.09	**<0.001**
Neuropsychiatric	0.81±0.18 (187)	0.87±0.16 (186)	0.06	**<0.001**	0.90±0.15 (146)	0.09	**<0.001**
Metabolic	0.86±0.18 (58)	0.88±0.18 (58)	0.02	0.115	0.92±0.16 (42)	0.06	**0.018**
EQ Visual Analogue Scale (0: worst; 100: best)							
Total	73.2±16.9 (300)	77.0±15.9 (299)	3.79	**<0.001**	80.2±15.0 (234)	6.98	**<0.001**
Gastrointestinal	74.9±14.7 (58)	77.9±15.0 (57)	3.00	0.184	81.2±14.2 (48)	6.22	**0.022**
Neuropsychiatric	72.3±17.3 (187)	76.8±16.4 (187)	4.46	**<0.001**	80.7±14.6 (147)	8.35	**<0.001**
Metabolic	73.9±16.2 (58)	77.0±14.5 (58)	3.06	0.308	77.8±16.3 (43)	3.86	0.165
MOS-HIV physical component (mean: 50; SD: 10)							
Total	52.1±7.6 (271)	56.6±6.2 (251)	4.52	**<0.001**	56.6±7.7 (211)	4.48	**<0.001**
Gastrointestinal	51.2±8.3 (48)	58.2±5.2 (48)	6.97	**<0.001**	57.3±7.2 (42)	6.07	**<0.001**
Neuropsychiatric	52.4±7.4 (175)	56.6±6.2 (161)	4.26	**<0.001**	56.7±7.6 (135)	4.34	**<0.001**
Metabolic	52.3±7.4 (52)	55.2±6.5 (46)	2.92	**0.002**	55.5±8.7 (37)	3.17	**0.010**
MOS-HIV mental component (mean: 50; SD: 10)							
Total	48.8±11.0 (271)	53.0±8.8 (251)	4.14	**<0.001**	54.0±8.7 (211)	5.17	**<0.001**
Gastrointestinal	49.5±9.7 (48)	53.7±7.8 (48)	4.18	**0.003**	54.2±7.5 (42)	4.65	**<0.001**
Neuropsychiatric	47.9±11.2 (175)	53.0±8.8 (161)	5.07	**<0.001**	53.8±9.2 (135)	5.89	**<0.001**
Metabolic	50.5±11.0 (52)	51.8±9.7 (46)	1.34	0.399	54.9±7.6 (37)	4.45	0.185

SD; Standard deviation p -Value ≤0.05 in bold

Table 3. Adherence (SMAQ) and satisfaction (ESTAR) according to previous intolerance (gastrointestinal, neuropsychiatric or metabolic).

	Baseline	**Week 4**			**Week 16**			**Week 32**			**Week 48**		
	n (%)	**n (%)**	**Difference**	***p*-Value**	**n (%)**	**Difference**	***p*-Value**	**n (%)**	**Difference**	***p*-Value**	**n (%)**	**Difference**	***p*-Value**
			(vs Baseline)			**(vs Baseline)**			**(vs Baseline)**			**(vs Baseline)**	
SMAQ: % adherent subjects (0%: worst; 100%: best)													
Total	164 (54.7)	189 (63.0)	8.3	**0.005**	167 (60.7)	6.0	0.081	169 (65.0)	10.3	**0.032**	149 (63.4)	8.7	**0.006**
Gastrointestinal	29 (50.0)	34 (65.4)	15.4	0.09	30 (56.6)	6.6	0.569	35 (63.6)	13.6	0.159	32 (68.1)	18.1	0.252
Neuropsychiatric	105 (58.3)	120 (64.2)	5.9	**0.021**	105 (66.9)	8.6	0.190	98 (63.6)	5.3	0.398	89 (64.0)	5.7	0.276
Metabolic	35 (63.6)	41 (71.9)	8.3	0.376	38 (66.7)	3.1	0.376	38 (76.0)	12.4	0.168	30 (76.9)	13.3	**0.019**
	Baseline	**Week4**			**Week 16**			**Week 32**			**Week 48**		
	Mean±SD (n)	**Mean±SD (n)**	**Difference**	***p*-Value**	**Mean±SD (n)**	**Difference**	***p*-Value**	**Mean±SD (n)**	**Difference**	***p*-Value**	**Mean±SD (n)**	**Difference**	***p*-Value**
			(vs Baseline)			**(vs Baseline)**			**(vs Baseline)**			**(vs Baseline)**	
ESTAR: Satisfaction with treatment (0: worst; 6: best)													
Total													
Ease	4.8±1.3 (296)	5.4±1.0 (298)	0.57	**<0.001**	5.4±0.9 (274)	0.58	**<0.001**	5.4±0.9 (259)	0.60	**<0.001**	5.4±0.8 (234)	0.65	**<0.001**
Convenience	5.0±1.4 (296)	5.6±0.7 (299)	0.65	**<0.001**	5.6±0.7 (274)	0.81	**<0.001**	5.6±0.7 (259)	0.58	**<0.001**	5.6±0.6 (234)	0.62	**<0.001**
Flexibility	4.8±1.3 (296)	5.2±1.1 (298)	0.35	**<0.001**	5.2±1.1 (274)	0.38	**<0.001**	5.3±1.0 (259)	0.44	**<0.001**	5.2±1.1 (234)	0.38	**<0.001**
Gastrointestinal													
Ease	4.5±1.4 (58)	5.3±1.0 (56)	0.73	**<0.001**	5.5±0.7 (56)	1.02	**<0.001**	5.3±0.9 (55)	0.77	**0.001**	5.5±0.7 (48)	0.96	**<0.001**
Convenience	4.0±1.7 (58)	5.5±0.9 (57)	1.44	**<0.001**	5.6±0.6 (56)	1.60	**<0.001**	5.5±0.7 (55)	1.50	**<0.001**	5.5±0.7 (48)	1.47	**<0.001**
Flexibility	4.5±1.4 (58)	5.1±1.0 (57)	0.64	**0.003**	5.2±1.0 (56)	0.76	**0.001**	5.4±0.8 (55)	0.90	**<0.001**	5.3±0.8 (48)	0.82	**<0.001**
Neuropsychiatric													
Ease	4.9±1.4 (183)	5.3±1.0 (187)	0.49	**<0.001**	5.3±1.0 (167)	0.42	**<0.001**	5.3±1.0 (157)	0.47	**<0.001**	5.4±0.8 (147)	0.55	**<0.001**
Convenience	5.3±1.1 (183)	5.6±0.8 (187)	0.25	**0.006**	5.6±0.7 (167)	0.23	**0.001**	5.5±0.8 (157)	0.15	**0.023**	5.6±0.6 (147)	0.27	**<0.001**
Flexibility	4.9±1.3 (183)	5.1±1.1 (186)	0.25	**0.020**	5.1±1.1 (167)	0.23	**0.016**	5.1±1.1 (157)	0.25	**0.009**	5.1±1.2 (147)	0.24	**0.008**
Metabolic													
Ease	4.9±1.2 (58)	5.5±0.8 (57)	0.65	**0.001**	5.3±1.1 (57)	0.47	**0.007**	5.6±0.7 (51)	0.75	**<0.001**	5.5±0.9 (43)	0.63	**0.013**
Convenience	4.8±1.5 (58)	5.8±0.5 (58)	1.00	**<0.001**	5.7±0.7 (57)	0.91	**<0.001**	5.7±0.6 (51)	0.92	**<0.001**	5.7±0.7 (43)	0.86	**<0.001**
Flexibility	4.8±1.4 (58)	5.4±0.8 (58)	0.54	**0.007**	5.3±1.1 (57)	0.42	**0.06**	5.5±0.8 (51)	0.65	**0.002**	5.4±0.9 (43)	0.51	**0.019**

SD; Standard deviation p -Value ≤0.05 in bold

Finally, the preferences for the new treatment (EVIPLERA®) compared with the previous cART are presented in Table **4**. In all patients, less than 2.0% of patients considered the new treatment to be worse (slightly or much worse) than the previous treatment.

3.3. PRO Data According to the Reason of Intolerance to the Previous cART

In the ACTG questionnaire, a statistically significant decrease was observed (p-value≤0.05) in the number of symptoms and degree of discomfort of these symptoms at week 48 visit compared with the baseline visit in the three groups of patients (except in patients with metabolic disturbances when assessed the number of symptoms). According to the results of the EQ-5D, the health status significantly improved (p-value≤0.05) both with respect to the social score and in the VAS results in the groups of patients who exhibited neuropsychiatric and gastrointestinal intolerances at the week 48 visit compared with the baseline visit. The patients with metabolic disturbances also exhibited improvement, although this improvement was not statistically significant in the VAS results.

In the MOS-HIV questionnaire, a statistically significant improvement (p-value≤0.05) was observed in the physical component in the three groups of patients between the week 48 visit and the baseline visit. Patients who exhibited neuropsychiatric and gastrointestinal also showed a statistically significant improvement (p-value≤0.05) in the mental component.

According to the results of SMAQ questionnaire (Table **3**), no significant differences exist (p-value>0.05) with respect to adherence between the week 48 visit and the baseline visit in the group of patients with neuropsychiatric and gastrointestinal intolerances. However, patients with metabolic disturbances showed significantly greater adherence (p-value≤0.05). In the week 48 visit, 68.1% of patients with gastrointestinal intolerance, 64.0% of patients with neuropsychiatric intolerances, and 76.9% of patients with metabolic disturbances were adherent. In spite of the restrictive test used, which may explain the low adherence reported, an undetectable viral load was maintained in 95.3% of the patients.

All groups of patients reported greater satisfaction with the ease, the convenience and the flexibility of use of the new treatment compared with the old treatment.

In the week 48 visit, 93.7% of patients with gastrointestinal intolerance, 86.4% of patients with neuropsychiatric intolerances, and 81.8% of patients with metabolic disturbances their new treatment was better (slightly or much better) than the previous regimen (Table **4**).

4. DISCUSSION

The PRO-STR study measured the impact of the change from a cART to EVIPLERA® in patients infected with HIV. The PRO-STR study was the first study, to our knowledge, to evaluate PRO based on intolerance to previous treatment.

Overall, the results of the study demonstrate that at week 48, switching to EVIPLERA® regimen from a previous NNRTI- or a PI-based regimen is associated with a significant decrease in the number of symptoms and in the degree of discomfort because of these symptoms. These results are consistent with those described in the study by Wilkins et al. in which the efficacy and safety of the 786 patients who changed their previous cART for an STR (EVIPLERA® or EFV/FTC/TDF) were evaluated. After 48 weeks of follow-up, an improvement in the symptoms reported by the patients was also observed [21]. Likewise, in another study that changed to EVIPLERA®, symptoms related to the central nervous system significantly decreased after 12 weeks [23]. However, none of the studies evaluated these symptoms as a function of previous intolerances.

Our study also demonstrated, utilizing the EQ-5D questionnaire that the general state of health significantly improved in the group of patients who presented neuropsychiatric and gastrointestinal intolerances. The patients with metabolic disturbances also exhibited improvements in their health status, although the results were not statistically significant. These data are consistent with a study performed in Italy demonstrating that, with the switch from EFV to RPV, patients reported an increased perceived general health evaluated using the VAS [24].

A study conducted in Spain with 328 patients using the specific MOS-HIV questionnaire [25] reported that the patients receiving an STR reported a better HRQoL than patients with other cART. The results of the PRO-STR study also indicated improvements with respect to the baseline visit to both, the physical and mental components of the MOS-HIV, except in the mental component the patients with metabolic disturbances, had an improvement but not significant.

Moreover, in the PRO-STR study, all groups of patients reported greater satisfaction with the ease, the convenience and the flexibility of use of the new treatment compared with the old treatment. Additionally, with respect to preferences, more than 85.9% of patients found their new treatment (EVIPLERA®) to be better than the previous one. In addition, at week 48, the PRO-STR study revealed improvements in the adherence to treatment, being statically significant in patients with metabolic disturbances.

This finding is consistent with other studies that have also demonstrated better results in satisfaction and preference with EVIPLERA® compared with the previous treatment [26].

In addition, we observed that the viral load remained undetectable at week 48 in the majority of the patients. Also, the proportion of patients with a CD4+ count greater than 500 cells/mm^3 increased significantly. In a study in which the efficacy and tolerability of EVIPLERA® was evaluated in 304 patients [27], viral suppression was maintained. Highleyman et al. confirmed these results, as all patients who changed from EFV/FTC/TDF to EVIPLERA® maintained their viral suppression after the change in treatment [23]. Another study comparing EFV with RPV demonstrated that the efficacy of RPV was not inferior to that of EFV [28]. Another study [29] demonstrated that RPV improved tolerability and quality of life versus EFV. Besides, the quality of life of patients was improved.

Table 4. Preference of treatment (compared to previous regimen).

-	Week 4	Week 16	Week 32	Week 48
	n (%)	n (%)	n (%)	n (%)
Total				
Much better	160 (53.3)	171 (62.2)	155 (59.6)	150 (63.8)
Slightly better	71 (23.7)	57 (20.7)	61 (23.5)	52 (22.1)
About the same	59 (19.7)	43 (15.6)	35 (13.5)	29 (12.3)
Slightly worse	4 (1.3)	2 (0.7)	6 (2.3)	1 (0.4)
Much worse	5 (1.7)	1 (0.4)	1 (0.4)	2 (0.9)
No data available	1 (0.3)	1 (0.4)	2 (0.8)	1 (0.4)
Gastrointestinal				
Much better	38 (65.5)	39 (69.6)	34 (61.8)	35 (72.9)
Slightly better	11 (19.0)	8 (14.3)	15 (27.3)	10 (20.8)
About the same	6 (10.3)	9 (16.1)	4 (7.3)	3 (6.3)
Slightly worse	2 (3.4)	0 (0.0)	2 (3.6)	0 (0.0)
Much worse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No data available	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Neuropsychiatric				
Much better	96 (51.3)	104 (61.9)	93 (58.9)	93 (63.3)
Slightly better	50 (26.7)	39 (23.2)	38 (24.1)	34 (23.1)
About the same	35 (18.7)	21 (12.5)	22 (13.9)	18 (12.2)
Slightly worse	2 (1.1)	2 (1.2)	2 (1.3)	1 (0.7)
Much worse	4 (2.1)	1 (0.6)	1 (0.6)	1 (0.7)
No data available	0 (0.0)	1 (0.6)	2 (1.3)	0 (0.0)
Metabolic				
Much better	31 (53.4)	35 (61.4)	32 (62.7)	26 (59.1)
Slightly better	8 (13.8)	10 (17.5)	7 (13.7)	10 (22.7)
About the same	18 (31.0)	10 (17.5)	10 (19.6)	6 (13.6)
Slightly worse	0 (0.0)	1 (1.8)	2 (3.9)	0 (0.0)
Much worse	1 (1.7)	1 (1.8)	0 (0.0)	1 (2.3)
No data available	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)

This study has several limitations that should be considered when interpreting the results. First, the PRO-STR study is based on Real World Evidence and no control group was available to compare to EVIPLERA®. However, the baseline visit was assumed as a control cohort and was used to compare the results obtained in the study with the previous phase. That is, prospective individual comparisons were done across visits. No comparisons were done either between the different groups of patients because some of the patients who exhibited more than one type of intolerance belonged to more than one group.

On the other hand, although the initial sample size was not reached, the statistical power in hypothesis tests allow to conclude that the differences observed in the sample are consistent.

Other limitations are the satisfaction improvement seen in the cohort study because are limited to EVIPLERA® and

for that, the generalization of the results to others STR should be cautious. In consequence, the results obtained for EVIPLERA® should not be extrapolated to other STRs. Although STRs like TDF/FTC/elvitegravir (EVG) /Cobi improves patient adherence and satisfaction [30, 31], there is no certainty (no studies available) that the same improvements occur with other new STRs now available in clinical practice such as dolutegravir-containing regimens.

Despite the limitations described above, the analysis of the PRO-STR study, performed in a real-world setting, demonstrates that patients infected with HIV who switched their previous cART to EVIPLERA® because of intolerances maintained their viral response and their CD4 count. Furthermore, throughout the 48 weeks of follow-up with EVIPLERA®, in the overall patient population and in most sub-groups a significant improvement in the presence and magnitude of symptoms was observed, reported HRQoL increased (significantly so in the group of patients with neuropsychiatric and gastrointestinal intolerances), and satisfaction with the new treatment improved in all groups). Adherence to treatment was maintained in patients with neuropsychiatric and gastrointestinal intolerances and improved significantly in metabolic ones. Besides, the preferences for the new treatment relative to the previous cART increased. To sum up, switching to EVIPLERA® has meant an improvement in patient-reported outcomes in HIV-infected patients while maintaining a good virological and immunological response.

In this era in which several once a day pill cART formulations are available, it would be of interest to assess PRO in patients receiving these new regimens.

CONCLUSION

The results of the study demonstrate that at week 48, switching to EVIPLERA® regimen from a previous NNRTI- or a PI-based regimen due to toxicity is associated with a significant decrease in the number of symptoms and in the degree of discomfort because of these symptoms. An improvement in HRQoL and preference with treatment was also observed. Apart from that, EVIPLERA® maintained a virological response, CD4+ cell count and maintained (in the group of patients with neuropsychiatric and gastrointestinal intolerances) or improved (in the group of patients with metabolic disturbances) adherence.

LIST OF ABBREVIATIONS

cART	=	Combined Antiretroviral Therapy
DRV/r	=	Darunavir boosted with ritonavir
EFV	=	Efavirenz
EVG	=	Elvitegravir
HAART	=	Highly Active Antiretroviral Therapy
HIV	=	Human Immunodeficiency Virus
HRQoL	=	Health-Related Quality-of-Life
NNRTI	=	Non-Nucleoside Reverse Transcriptase Inhibitor
PI	=	Protease Inhibitor
PRO	=	Patient-Reported Outcomes
RPV/FTC/TDF	=	Rilpivirine /emtricitabine /tenofovir
STRs	=	Single-Tablet Regimens
VAS	=	Visual Analogue Scale

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was evaluated and approved by the Institutional Review Boards of the participating centers.

HUMAN AND ANIMAL RIGHTS

No animals were used in the study. All humans research procedures followed were in accordance with the standards set forth in the Declaration of Helsinki principles of 1975, as revised in 2008 (http://www.wma.net/en/20activities/10 ethics/10helsinki/).

CONSENT FOR PUBLICATION

Written informed consents were obtained from all participants.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

APPENDIX I. WRITING GROUP: PRO-STR STUDY

1. Hospital Universitari de Bellvitge (Cataluña). Dr. Daniel Podzamczer Palter.
2. Hospital Virgen de la Victoria (Andalucía). Dr. Jesús Santos González.
3. Hospital de Especialidades de Puerto Real (Andalucía). Dr. Alberto Romero Palacios.
4. Hospital Carlos Haya (Andalucía). Dr. Maria Isabel Mayorga Mayorga.
5. Hospital Universitario Virgen de las Nieves (Andalucía). Dr. Juan Pasquau Liaño.
6. Complejo Hospitalario Universitario de Albacete (Castilla la Mancha). Dr. Elisa Martínez Alfaro.
7. Hospital Virgen de la Salud (Castilla la Mancha). Dr. María Antonia Sepúlveda.
8. Hospital Nuestra Sra. del Prado (Castilla la Mancha). Dr. Miguel Yzusqui.
9. Complejo Hospitalario La Mancha Centro (Castilla la Mancha). Dr. José Ramón Barberá Farré.
10. Hospital General Virgen de la Luz (Castilla la Mancha). Dr. Paloma Geijo Martínez.
11. Hospital Universitario de Guadalajara (Castilla la Mancha). Dr. Manuel Rodríguez Zapata.
12. Hospital Universitario del Río Hortega (Castilla y León): Dr. Pablo Bachiller Luque.
13. Hospital del Bierzo (Castilla y León). Dr. Alberto Bahamonde Carrasco.
14. Hospital General de Burgos (Castilla y León). Dr. Juan Francisco Lorenzo.
15. Hospital del Mar (Cataluña). Dr. Hernando Knobel.
16. Hospital General de Granollers (Cataluña). Dr. Elisabeth Deig Comerma.
17. Hospital Vall d´Hebrón (Cataluña). Dr. Ariadna Torrella.
18. Hospital de la Santa Creu y Sant Pau (Cataluña). Dr. Pere Domingo.
19. Hospital Universitari Germans Trias i Pujol (Cataluña). Dr. Bonaventura Clotet.
20. Hospital Dr. Josep Trueta de Girona (Cataluña). Dr. Xavier Salgado Serrano.
21. Complejo Hospitalario Universitario de Santiago (Galicia). Dr. Antonio Antela López.
22. Hospital Xeral de Vigo (Galicia). Dr. Celia Miralles Álvarez.
23. Hospital Montecelo (Galicia). Dr. Julio Diz Arén.
24. Hospital Can Misses de Ibiza (Islas Baleares). Dr. Pedro Fernández.
25. Hospital Mateu Orfila (Islas Baleares). Dr. Eduardo Rodríguez de Castro Hurtado.

REFERENCES

[1] Johnson LF, Mossong J, Dorrington RE, *et al*. International Epidemiologic Databases to Evaluate AIDS Southern Africa Collaboration. Life expectancies of South African adults starting antiretroviral treatment: collaborative analysis of cohort studies. PLoS Med 2013; 10: e1001418.

[2] Nakagawa F, May M, Phillips A. Life expectancy living with HIV: recent estimates and future implications. Curr Opin Infect Dis 2013; 26: 17-25.

[3] Clay PG, Nag S, Graham CM, *et al*. Meta-Analysis of Studies Comparing Single and Multi-Tablet Fixed Dose Combination HIV Treatment Regimens. Medicine 2015; 94: e1677.

[4] Blanco JL, Montaner JS, Marconi VC, *et al*. Lower prevalence of drug resistance mutations at first-line virological failure to first-line therapy with atripla *vs.* tenofovir + emtricitabine/lamivudine + efavirenz administered on a multiple tablet therapy. AIDS 2014; 28: 2531-9.

[5] Cohen CJ, Meyers JL, Davis KL. Association between daily antiretroviral pill burden and treatment adherence, hospitalisation risk, and other healthcare utilisation and costs in a US medic aid population with HIV. BMJ Open 2013; 3: e003028.

[6] Lin MK, Wu AW, Revicki DA. Incorporating quality of life measures in HIV clinical trials. HIV Clin Trials 2002; 3: 202-18.

[7] Clayson DJ, Wild DJ, Quarterman P, *et al*. A comparative review of health-related quality-of-life measures for use in HIV/AIDS clinical trials. Pharmacoeconomics 2006; 24: 751-65.

[8] Mafirakureva N, Dzingirai B, Postma MJ, van Hulst M, Khoza S. Health-related quality of life in HIV/AIDS patients on antiretroviral therapy at a tertiary care facility in Zimbabwe. AIDS Care 2016; 21: 1-9.

[9] Simpson KN, Hanson KA, Harding G, *et al*. Patient reported outcome instruments used in clinical trials of HIV-infected adults on NNRTI-based therapy: a 10-year review. Health Qual Life Outcomes 2013; 11: 164.

[10] Cunningham SD, Card JJ. Realities of replication: implementation of evidence-based interventions for HIV prevention in real-world settings. Implement Sci 2014*;* 9: 5.

[11] National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Rockville: National Cancer Institute; 2010. Available in: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. [Accessed on May 27, 2016]

[12] Regnault A, Marfatia S, Louie M, *et al*. Satisfactory cross-cultural validity of the ACTG symptom distress module in HIV-1-infected antiretroviral-naive patients. Clin Trials 2009; 6: 574-84.

[13] EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy 1990; 16: 199-208.

[14] Badia X, Roset M, Monserrat S, *et al*. La versión española del EuroQol: descripción y aplicaciones. Med Clin (Barc) 1999; 112: 79-85.

[15] Herdman M, Badia X, Berra S. El EuroQol-5D: una alternativa sencilla para la medición de la calidad de vida relacionada con la salud en atención primaria. Aten Primaria 2001; 6: 425-30.

[16] Badía X, Podzamczer D, López-Lavid C, *et al*. Evidence-based medicine and the validation of quality-of-life questionnaires: the Spanish version of the MOS-HIV questionnaire for the evaluation of the quality of life in patients infected by HIV. Enferm Infecc Microbiol Clin 1999; 17: 103-13.

[17] Badía X, Podzamczer D, Casado A, *et al*. Evaluating changes in health status in HIV-infected patients: Medical Outcomes Study-HIV and Multidimensional Quality of Life-HIV quality of life questionnaires. Spanish MOS-HIV and MQOL-HIV Validation Group. AIDS 2000; 14: 1439-47.

[18] Knobel H, Alonso J, Casado JL, *et al*. GEEMA Study Group Validation of a simplified medication adherence questionnaire in a large cohort of HIV-infected patients: the GEEMA Study. Aids 2002; 16: 605-13.

[19] Ventura JM, Casado MA, Morales JM, *et al*. Características psicométricas de la escala de satisfacción con el tratamiento antirretroviral (ESTAR): Estudio ARPAS (I). Farm Hosp 2007; 31: 331-9.

[20] Ventura JM, Casado MA, Escobar I, *et al*. Preferencias, satisfacción y adherencia con el tratamiento antirretroviral. Estudio AR-PAS (II). Farm Hosp 2007; 31: 340-52.

[21] Wilkins EL, Cohen CJ, Trottier B, *et al*. Patient-reported outcomes in the single-tablet regimen (STaR) trial of rilpivirine/ emtricitabine/tenofovirdisoproxil fumarate versus efavirenz/ emtricitabine/ tenofovirdisoproxil fumarate in antiretroviral treatment-naive adults infected with HIV-1 through 48 weeks of treatment. AIDS Care 2016; 28: 401-8.

[22] Hodder SL, Mounzer K, Dejesus E, *et al*. AI266073 Study Group. Patient-reported outcomes invirologically suppressed, HIV-1-Infected subjects after switching to a simplified, single-tablet regimen of efavirenz, emtricitabine, and tenofovir DF. AIDS Patient Care STDS 2010; 24: 87-96.

[23] Highleyman L. Switching from Atripla to Eviplera reduces central nervous system side-effects. Poster presented at 53rdInterscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). 23 September 2013.

[24] Di Matteo S, Bruno GM, Astuti N, *et al*. Switching from an EFV-Based STR to an RPV-Based STR is Effective, Safe and Improves HIV Patients Health Status. Value Health 2014; 17: A677-8.

[25] Ventura Cerdá JM, Martín Conde MT, Morillo Verdugo R *et al*. Adherence, satisfaction and health-related quality of life in HIV-infected patients with antiretroviral therapy in Spain. The ARPAS study. Farm Hosp 2014; 38: 291-9.

[26] Brunetta J, Moreno Guillén S, Antinori A, *et al*. Patient-reported outcomes after a switch to a single-tablet regimen of rilpivirine, emtricitabine, and tenofovir DF in HIV-1-positive, virologically suppressed individuals: Additional findings from a randomized, open-label, 48-week trial. Patient 2015; 8: 257-67.

[27] Cazanave C, Reigadas S, Mazubert C, *et al*. Switch to Rilpivirine/Emtricitabine /Tenofovir Single-Tablet Regimen of Human Immunodeficiency Virus-1 RNA-Suppressed Patients, Agence Nationale de Recherches sur le SIDA et les Hépatites Virales CO3 Aquitaine Cohort, 2012-2014. Open Forum Infect Dis 2015; 12; 2(1): ofv018.

[28] Cohen CJ, Andrade-Villanueva J, Clotet B, *et al*. THRIVE study group. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. Lancet 2011; 378: 229-37.

[29] Van Lunzen J, Antinori A, Cohen CJ, *et al*. Rilpivirine vs. efavirenz-based single-tablet regimens In treatment-naive adults: week 96 efficacy and safety from a randomized phase 3bstudy. AIDS 2016; 30: 251-9.

[30] Gathe J, Arribas JR, Van Lunzen J, *et al*. Patient-reported symptoms over 48 weeks in a randomized, open-label,phase 3b non-inferiority trial of adults with HIV switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir DF versus continuation of ritonavir-boosted protease inhibitor with emtricitabine and tenofovir DF. Patient 2015; 8: 445-54.

[31] Prinapori R, Di Biagio A. Efficacy, safety, and patient acceptability of elvitegravir/cobicistat/emtricitabine/tenofovir in the treatment of HIV/AIDS. Patient Prefer Adherence 2015; 9: 1213-8.