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Effectiveness of the combination elvitegravir/cobicistat/tenofovir/emtricitabine (EVG/COB/TFV/FTC) plus darunavir among treatment-experienced patients in clinical practice: a multicentre cohort study

Inés Suárez-García[1,2,3*], Cristina Moreno[4], Marta Ruiz-Algueró[4], María Jesús Pérez-Elías[5], Marta Navarro[6], Marcos Díez Martínez[7], Pompeyo Viciana[8], Laura Pérez-Martínez[9], Miguel Górgolas[10], Concha Amador[11], Miguel Alberto de Zárraga[12], Inma Jarrín[4] and the Cohort of the Spanish HIV/AIDS Research Network (CoRIS)

Abstract

Background: The aim of this study was to investigate the effectiveness and tolerability of the combination elvitegravir/cobicistat/tenofovir/emtricitabine plus darunavir (EVG/COB/TFV/FTC + DRV) in treatment-experienced patients from the cohort of the Spanish HIV/AIDS Research Network (CoRIS).

Methods: Treatment-experienced patients starting treatment with EVG/COB/TFV/FTC + DRV during the years 2014–2018 and with more than 24 weeks of follow-up were included. TFV could be administered either as tenofovir disoproxil fumarate or tenofovir alafenamide. We evaluated virological response, defined as viral load (VL) < 50 copies/ml and < 200 copies/ml at 24 and 48 weeks after starting this regimen, stratified by baseline VL (< 50 or ≥ 50 copies/ml at the start of the regimen).

Results: We included 39 patients (12.8% women). At baseline, 10 (25.6%) patients had VL < 50 copies/ml and 29 (74.4%) had ≥ 50 copies/ml. Among patients with baseline VL < 50 copies/ml, 85.7% and 80.0% had VL < 50 copies/ml at 24 and 48 weeks, respectively, and 100% had VL < 200 copies/ml at 24 and 48 weeks. Among patients with baseline VL ≥ 50 copies/ml, 42.3% and 40.9% had VL < 50 copies/ml and 69.2% and 68.2% had VL < 200 copies/ml at 24 and 48 weeks. During the first 48 weeks, no patients changed their treatment due to toxicity, and 4 patients (all with baseline VL ≥ 50 copies/ml) changed due to virological failure.

Conclusions: EVG/COB/TFV/FTC + DRV was well tolerated and effective in treatment-experienced patients with undetectable viral load as a simplification strategy, allowing once-daily, two-pill regimen with three antiretroviral drug classes. Effectiveness was low in patients with detectable viral loads.

Keywords: HIV infection, Highly active antiretroviral therapy, Cohort studies, Darunavir

Background

Treatment adherence is crucial for the effectiveness of antiretroviral therapy (ART) among HIV-infected patients. Adherence could be impaired with antiretroviral regimens that entail multiple pills or more than

*Correspondence: inessuarez@hotmail.com
[1] Department of Internal Medicine, Infectious Diseases Group, Hospital Universitario Infanta Sofía, Paseo de Europa, 34. San Sebastián de los Reyes, 28702 Madrid, Spain
Full list of author information is available at the end of the article

once-daily dosing [1]; this is a frequent situation among patients with drug-resistant HIV. Simplification of complex ART regimens is an important strategy for reducing the number of pills or doses per day and is intended to improve patients' adherence and quality of life without compromising treatment effectiveness [2].

The fixed-dose combinations elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine (EVG/COB/TDF/FTC, Stribild®) and elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine (EVG/COB/TAF/FTC, Genvoya®) have been extensively used for the treatment of HIV-infected adults [3, 4]. The association of one of those fixed-dose combinations with darunavir 800 mg (DRV) would allow a once-daily, two-pill regimen that includes three classes of antiretroviral drugs and could be used to treat selected patients with drug-resistant HIV. This is an off-label indication.

With these combinations, COB, which boosts EVG, would also allow boosting of DRV [5]. However, pharmacokinetic studies evaluating drug levels in patients receiving EVG/COB/TDF/FTC plus DRV have found conflicting results. While some studies have found lower levels of DRV and EVG in patients receiving EVG/COB/TDF/FTC + DRV compared to those receiving each drug as a separate component (DRV being boosted either with COB or ritonavir) [6, 7], others found similar DRV and EVG levels in patients receiving this combination compared to those receiving each separate drug [8, 9]. All these studies involved a very low number of patients (between 5 and 24).

The efficacy of EVG/COB/TAF/FTC + DRV in virologically suppressed patients was demonstrated in an open-label clinical trial, which showed that switching to EVG/COB/TAF/FTC + DRV was non-inferior to maintaining the previous ART at 24 weeks and superior at 48 weeks [10]. However, in spite of the results of this clinical trial and the potential advantages of this combination for ART simplification, there is very little evidence in real-life clinical practice. Only three single-centre cohort studies analysing EVG/COB/TDF/FTC + DRV have been published, involving a very low number of patients (21, 10, and 17 patients) and with limited follow-up [5, 6, 11].

Given the very scarce evidence with the combinations EVG/COB/TDF/FTC + DRV and EVG/COB/TAF/FTC + DRV in clinical practice, the conflicting results of pharmacokinetic studies, and the potential advantages of these combinations as a simplification strategy, we designed a study to describe the use of elvitegravir/cobicistat/tenofovir (administered either as disoproxil fumarate or alafenamide)/emtricitabine plus darunavir 800 mg (EVG/COB/TFV/FTC + DRV) and analyse its effectiveness and tolerability in the multicentre Cohort of the Spanish HIV/AIDS Research Network (CoRIS). The specific objectives of the study were: (1) to describe the patients initiating EVG/COB/TFV/FTC + DRV and the reasons for starting this regimen, (2) to describe the toxicity of this regimen among patients who stopped it due to adverse events, and (3) to describe the effectiveness of EVG/COB/TFV/FTC + DRV in terms of viral suppression and change in CD4 count at 24 and 48 weeks after starting this regimen.

Methods

Patients were selected from the Cohort of the Spanish HIV/AIDS Research Network (CoRIS), which has been described in detail elsewhere [12, 13]. CoRIS is a prospective multicentre cohort of adult HIV-positive treatment-naïve patients, recruited from 46 centres from 13 Autonomous Regions in the Spanish public healthcare system. Since January 2004 to the last update in November 2018, 15509 patients have been recruited in CoRIS.

We included all treatment-experienced patients who started treatment with EVG/COB/TFV/FTC + DRV from January 2014 to November 2018 and who had more than 24 weeks of follow-up. TFV could be administered either as tenofovir disoproxil fumarate or tenofovir alafenamide.

We collected information on the following variables: age, sex, mode of HIV transmission (men who have sex with men [MSM], heterosexual, injecting drug user [IDU], other/unknown), country of origin (Spanish, foreign-born), CD4 count and viral load at the start of EVG/COB/TFV/FTC + DRV and at 24 and 48 weeks after starting this regimen (± 12 weeks), reasons for stopping the previous treatment and EVG/COB/TFV/FTC + DRV (simplification, virological failure, toxicity, interactions, other, unknown) and regimen to which it was switched, previous antiretroviral regimens, number of pills and doses per day with the previous antiretroviral regimen, and time since the start of the first ART.

Descriptive analyses were carried out using frequency tables for categorical variables and median and interquartile range (IQR) for continuous variables. For the analysis of treatment effectiveness, the primary endpoint was the proportion of patients with virological response, defined as viral load < 50 copies/ml at 24 and 48 weeks after starting EVG/COB/TFV/FTC + DRV. Since the threshold of 200 copies/ml is used in several guidelines to define virologic failure [14, 15], we also analysed a secondary endpoint of virological response defined as viral load < 200 copies at 24 and 48 weeks. We also evaluated the median change in CD4 count at 24 and 48 weeks, and the proportion of patients stopping their treatment due to virological failure and due to adverse events. Results were stratified by baseline viral load (< 50 or ≥ 50 copies/

ml): baseline was defined as the time of the initiation of EVG/COB/TFV/FTC + DRV. For the endpoints of virological response and change in CD4 count, we performed an intention to treat analysis: therefore, once the treatment was started, all patients were assumed to remain on it and subsequent changes were ignored.

Statistical analyses were performed in Stata software (version 14.0; Stata Corporation, College Station, Texas, USA). All patients signed informed consent forms. The study was approved by the Ethics Committee of Instituto de Salud Carlos III (Madrid).

Results

During the study period, 39 patients from 11 centres switched their ART to the regimen EVG/COB/TFV/FTC + DRV. Patients' demographic and clinical characteristics are shown in Table 1. At the start of the regimen, tenofovir was administered as TDF in 16 and as TAF in 23 patients. During follow-up, eight of the 16 patients who started the regimen with TDF switched TDF to TAF as part of the same regimen.

At baseline, 10 (25.6%) patients were virologically suppressed and 29 (74.4%) patients had detectable viral load. The most frequent reasons for changing to this regimen were virological failure and treatment simplification (Table 1).

The patients received EVG/COB/TFV/FTC + DRV for a median of 391 (IQR: 205 to 514) days. Outcomes at 24 and 48 weeks are shown in Table 2.

Among virologically suppressed patients at baseline, 85.7% and 80.0% of the patients achieved viral load < 50 copies/ml at 24 and 48 weeks, respectively. However, among patients with detectable baseline viral load, only 42.3% and 40.9% achieved these endpoints, respectively. The percentages of patients achieving viral load < 200/ml at 24 and 48 weeks were higher for both groups and reached 100% among the patients who were virologically suppressed at baseline.

The number of patients who changed their treatment during the first 24 and 48 weeks, stratified by baseline viral load, is shown in Table 2. Among the two virologically suppressed patients at baseline who changed their treatment during the first 48 weeks, the reasons were simplification in 1 patient and unknown in 1 patient. Among patients with baseline detectable viral load, the reasons for changing the regimen during the first 24 weeks were failure in 4, simplification in 3, and non-adherence in 1 patient, and the reasons for changing the regimen during the first 48 weeks were simplification in 7 patients, failure in 4 patients, non-adherence in 1 patient, and unknown in 1 patient.

Table 1 Patients' characteristics at the start of EVG/COB/TFV/FTC + DRV (n = 39)

Age, median (IQR), years	**42 (34–50)**
Female	5 (12.8)
Mode of transmission	
Men who have sex with men	19 (48.7)
Heterosexual	13 (33.3)
Injecting drug user	5 (12.8)
Other/unknown	2 (5.1)
Geographic origin	
Spanish	14 (33.3)
Foreign-born	24 (61.5)
Unknown	1 (2.4)
Viral load, median (IQR), copies/ml	379 (40–12,000)
CD4 count, median (IQR), cells/microl	437 (108–740)
Viral load	
< 50 copies/ml	10 (25.6)
≥ 50 copies/ml	29 (74.4)
Years since starting ART, median (IQR)	5.3 (2.5–7.5)
Number of prior regimens, median (IQR)	3 (2–6)
Previous ART regimen	
ART daily pill burden, median (IQR)	2 (1–5)
At least 3 pills per day	17 (43.6)
At least twice daily ART dosing	11 (28.2)
Reasons for switching to EVG/COB/TFV/FTC + DRV	
Virologic failure	14 (35.9)
Simplification	10 (25.6)
Toxicity	4 (10.3)
Non-adherence	2 (5.1)
Unknown	9 (23.1)

Values are expressed as n/total (%) unless stated otherwise

IQR Interquartile range

Discussion

This study has analysed the largest cohort published to date showing results from "real-world" clinical practice with the regimen EVG/COB/TFV/FTC + DRV. In our study, EVG/COB/TFV/FTC + DRV was well tolerated and effective in treatment-experienced patients with baseline undetectable viral load as a simplification strategy, allowing a once-daily, two-pill regimen with three antiretroviral drug classes. However, effectiveness was low in patients with baseline detectable viral loads.

There is only one open-label clinical trial that assessed the efficacy of this regimen, which analysed 135 treatment-experienced, virologically suppressed patients who were randomized to continue their previous ART or change to EVG/COB/TAF/FTC + DRV. The study found that this combination had high efficacy (96.6%) and was noninferior to maintaining the

Table 2 Outcomes of patients at 24 and 48 weeks after starting EVG/COB/TFV/FTC + DRV, stratified by viral load at the start of the regimen

Outcome	24 weeks	48 weeks
Virological response < 50 copies/ml		
Viral load < 50 copies/ml	6/7 (85.7)	4/5 (80.0)
Viral load ≥ 50 copies/ml	11/26 (42.3)	9/22 (40.9)
Virological response < 200 copies/ml		
Viral load < 50 copies/ml	7/7 (100.0)	5/5 (100.0)
Viral load ≥ 50 copies/ml	18/26 (69.2)	15/22 (68.2)
CD4 change, cells/microl: median (IQR)		
Viral load < 50 copies/ml	29 (14–48)	8 (− 85–50)
Viral load ≥ 50 copies/ml	− 6 (− 134–107)	− 16 (− 116–77)
Patients stopping the regimen for any reason		
Viral load < 50 copies/ml	0/10 (0)	2/10 (20.0)
Viral load ≥ 50 copies/ml	8/29 (27.6)	13/29 (44.8)
Patients stopping the regimen due to treatment failure		
Viral load < 50 copies/ml	0/10 (0)	0/10 (0)
Viral load ≥ 50 copies/ml	4/29 (13.8)	4/29 (13.8)
Patients stopping the regimen due to toxicity		
Viral load < 50 copies/ml	0/10 (0)	0/10 (0)
Viral load ≥ 50 copies/ml	0/29 (0)	0/29 (0)

Values are expressed as n/total (%) unless stated otherwise

IQR Interquartile range

previous ART at 24 weeks and superior at 48 weeks [10]. However, it is necessary to contrast the findings from clinical trials with real-world data, such as those obtained from cohort studies: clinical trials include selected patients that are often different from those of the population who will receive those treatments (such as lower number of patients with severe immunosuppression, elderly patients, or those with co-morbidities), and provide more intensive monitoring to the patients (which could influence adherence to treatment and detection of adverse effects), limiting the generalizability of their findings [16, 17].

Regarding real-world data, the evidence for the effectiveness of this regimen is very limited: only three cohort studies have been published analysing EVG/COB/TDF/FTC + DRV, all from single centres, involving a very low number of patients, and analysing different endpoints. The effectiveness was high in the three studies: Naccarato et al. evaluated 21 treatment-experienced patients (29% of which were virologically suppressed before the switch) who received EVG/COB/TDF/FTC + DRV: at week 48, 14 (67%) patients had undetectable viral load, 1 had virologic failure (> 40 copies/ml) and 6 had stopped the treatment or had no viral load data [5]. Harris et al. evaluated the simplification to the same regimen in 10 virologically suppressed patients: 8 of them had viral loads < 40 copies/ml at weeks 24 and 48 and all of them had viral loads < 200 copies/ml up to week 48 [6]. The last study by Diaz et al. found that 15 (88%) of 17 patients (naïve and treatment-experienced) had viral loads < 50 copies/ml at week 24 [11].

In our study, the effectiveness of EVG/COB/TFV/FTC + DRV was high in patients who were virologically suppressed at baseline: 85.7% and 80.0% of the patients had viral loads < 50 copies at 24 and 48 weeks, respectively, and 100% of the patients had viral loads < 200 copies/ml at 24 and 48 weeks. These results are comparable to the studies mentioned above. However, the effectiveness was much lower for patients who had detectable viral loads at baseline. These results suggest that this regimen has high effectiveness as a switch strategy for virologically suppressed patients, but it should not be used in patients with virological failure if other alternatives exist. Overall, the treatment was well tolerated in both groups, as none of the patients discontinued their treatment due to toxicity. The treatment also allowed to decrease the pill burden in 43.6% of the patients and the number of doses per day in 28.2%.

For the combination EVG/COB/TFV/FTC + DRV, our patients were receiving tenofovir either as alafenamide or as disoproxil fumarate. Also, as EVG/COB/TAF/FTC was commercialized in Spain in May 2016, many patients who were receiving EVG/COB/TDF/FTC changed their treatment to EVG/COB/TAF/FTC in order to minimize the

risk of renal and bone toxicity, as did 8 of our patients. Given that the treatment with EVG/COB/TAF/FTC has shown non-inferiority compared to EVG/COB/TDF/FTC in clinical trials [3, 4], we have analysed our results combining both treatments. To ensure that this was an adequate strategy, we repeated our analysis stratifying by treatment with TAF or TDF: the results were not changed (data not shown).

Our study has the limitation of low sample size. Also, since CoRIS does not routinely record resistance testing in pre-treated patients, we could not describe accumulated resistance mutations or those arising after failure with this regimen. Another limitation is that we cannot give information on patients' adherence as CoRIS does not routinely record this variable. However, this is the largest cohort published to date analysing this treatment regimen, with a reasonable follow-up time, and it gives information from routine clinical practice for a combination that could be potentially useful for treatment simplification and has very little published evidence. Our strengths include the use of a multicentre cohort with rigorous quality control and which has clinical and demographic characteristics that are similar to the ones from the general population reported by the National HIV Surveillance System [18].

Conclusion

The combination EVG/COB/TFV/FTC + DRV is an effective, well tolerated strategy for treatment simplification in virologically suppressed patients. This treatment is not suitable, however, for treatment-experienced individuals with detectable viral loads, given the low efficacy in this group of patients.

Abbreviations

ART: Antiretroviral therapy; CoRIS: Cohort of the Spanish HIV/AIDS Research Network; DRV: Darunavir; EVG/COB/TAF/FTC: Elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine; EVG/COB/TDF/FTC: Elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine; EVG/COB/TFV/FTC: Elvitegravir/cobicistat/tenofovir/emtricitabine; IDU: Injecting drug user; IQR: Interquartile range; MSM: Men who have sex with men; VL: Viral load.

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Fieldwork data management and analysis: Inmaculada Jarrin, Belén Alejos, Cristina Moreno, Carlos Iniesta, Luis Miguel Garcia Sousa, Nieves Sanz Perez, Marta Rava.

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Authors' contributions

All authors were involved in the setting up of the cohort and contributed to its design. All authors were involved in data collection. ISG asked the research question presented in this paper and designed the study. ISG and CM performed the statistical analyses. ISG wrote the first draft of the paper which was supervised by IJ. All authors were involved in interpretation of the data and commented on interim drafts. All authors read and approved the final manuscript.

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Availability of data and materials

The authors confirm that, for approved reasons, some access restrictions apply to the data underlying the findings. Data cannot be made publicly available because they are owned by a third party, the HIV/AIDS Research Network (RIS), and because participants agreed that data would only be used for research projects by RIS or those projects approved by its Executive and Scientific Committee. Interested readers may send requests for the data to proyectoscoris@gmail.com. Requests will be assessed by the Executive and Scientific Committee.

Ethics approval and consent to participate

Ethics approval was obtained from all hospitals' Ethics Committees and every patient provided written informed consent to participate in the cohort. This study was approved by the Ethics Committee of Instituto de Salud Carlos III, Madrid, Spain.

Consent for publication

Not applicable.

Competing interests

ISG has received conference grants or speaker fees from BMS, ViiV Healthcare and Gilead. IJ has received teaching fees from ViiV Healthcare. All other authors declare that they have no conflict of interest related to this work.

Author details

[1] Department of Internal Medicine, Infectious Diseases Group, Hospital Universitario Infanta Sofía, Paseo de Europa, 34. San Sebastián de los Reyes, 28702 Madrid, Spain. [2] FIIB HUIS HHEN, Madrid, Spain. [3] Universidad Europea, Madrid, Spain. [4] Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Madrid, Spain. [5] Hospital Universitario Ramón y Cajal, Madrid, Spain. [6] Corporació Sanitària Parc Taulí, Barcelona, Spain. [7] Hospital General Universitario de Alicante, Alicante, Spain. [8] Hospital Virgen del Rocío, Sevilla, Spain. [9] Hospital San Pedro Centro de Investigación Biomédica de La Rioja (CIBIR), Logroño, La Rioja, Spain. [10] Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain. [11] Hospital de la Marina Baixa, La Vila Joiosa, Spain. [12] Hospital San Agustín, Avilés, Spain.

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