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Observational study to evaluate discontinuation of monotherapy with cobicistat-boosted darunavir in patients with human immunodeficiency virus

Antonio Solana-Altabella, PharmD[a,b,*], Emilio Monte-Boquet, PharmD, PhD[a], Marta Montero, MD[c], Pablo Pérez-Huertas, PharmD[a], Maria Jesús Cuéllar-Monreal, PharmD, PhD[a], Miguel Salavert, MD, PhD[c], José Luis Poveda-Andrés, PharmD, PhD[a]

Abstract

To evaluate the reasons for changing to monotherapy with protease inhibitors, together with the proportion and reasons for the interruption to treatment, in patients who have been treated at some point with cobicistat-boosted darunavir (DRV/c). Outpatients in a tertiary hospital. Observational retrospective study to evaluate monotherapy with DRV/c (800 mg/150 mg) in adult patients with human immunodeficiency virus infection, from December 2014 to July 2022. Demographic variables, viral load, cluster of differentiation 4 lymphocyte lymphocyte count, and antiretroviral therapy were assessed. 42 patients were included. 36% of the patients were undergoing monotherapy at the time of the analysis. The main reason for discontinuation was poor adherence. At time of analysis, 80% of the patients in monotherapy had an undetectable viral load. Antiretroviral therapy recommendations advise against exposing the patient to functional monotherapy with a single drug due to the high risk of virological failure and the onset of resistance to a single drug. Following the analysis of the results, DRV/c in monotherapy is not an effective strategy in the medium and long term due to factors such as lack of adherence or virological failure, although it can be maintained in specific circumstances. Therefore, patients undergoing monotherapy require close monitoring.

Abbreviations: 3TC = lamivudine, AEs = adverse events, ART = antiretroviral therapy, CD4 = cluster of differentiation 4 lymphocyte, DRV/c = darunavir with cobicistat, DRV/r = darunavir with ritonavir, DTG = dolutegravir, GeSIDA = spanish acquired immunodeficiency syndrome study group, HIV = human immunodeficiency virus, INSTI = integrase inhibitor, LPV/r = lopinavir with ritonavir, PI = boosted protease inhibitor, SD = standard deviation, VF = virological failure.

Keywords: monotherapy, darunavir, cobicistat, retrospective, effectiveness, adherence

1. Introduction

Since the introduction of antiretroviral therapy (ART) in 1996, the natural progression of human immunodeficiency virus (HIV) that, in most cases, led to the death of the patient, has successfully been slowed. This has allowed the evolution to disease chronicity, which has resulted in an increase in the time that patients are exposed to ART.

Despite its clear benefits, ART presents certain potential drawbacks such as the appearance of adverse events (AEs), and therefore there is the potential to simplify the therapy in patients with maintained virological stability. The appearance of possible AEs in the long term led to different organisms and work groups raising the question about the benefit of simplifying the treatment (monotherapy). However, the latest updates of the *Spanish National AIDS Plan Consensus Document on Antiretroviral Therapy in Adults Infected by the Human Immunodeficiency Virus* (Spanish acquired immunodeficiency syndrome study group [GeSIDA] guidelines), of January 2022, recommend against the use of dolutegravir (DTG), an integrase inhibitor (INSTI), in monotherapy due to the risk of virological failure (VF). Likewise, the guidelines also advise against prescribing darunavir with ritonavir (DRV/r), a boosted protease inhibitor (PI), in monotherapy due to the greater risk of virological resurgence.[1] This has led to the majority of Spanish physicians abandoning treatment with monotherapy.

Currently, different studies have shown a high rate of VF associated with RM choice in the integrase gene in patients who

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

The study was approved by the local Clinical Research Ethics Committee of Hospital Universitario y Politécnico La Fe, in accordance with the principles of the Declaration of Helsinki.

[a] Pharmacy Department, Hospital Universitario y Politécnico La Fe, [b] Instituto de Investigación Sanitaria La Fe (IISLAFE), [c] Infectious Disease Unit, Hospital Universitario y Politécnico La Fe.

** Correspondence: Antonio Solana-Altabella, Pharmacy Department. Hospital Universitario y Politécnico La Fe (e-mail: solana_ant@gva.es).*

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have changed their ART to monotherapy with DTG,[2,3] and therefore prescribing INSTI monotherapy is not recommended and has only been used in a clinical trial context.

Furthermore, monotherapy with DRV/r has not shown non-inferiority in the long term versus triple therapy in intention-to-treat analyses when the change to randomized therapy is also considered failure.[3–5] Non-inferiority has been shown in pure intention-to-treat analyses (ignoring different variables that may have an effect).[1] In a randomized open-label trial in patients with various previous RMs undergoing PI-based triple therapy, the change to dual therapy with PI + lamivudine (3TC) was virologically more effective than the change to monotherapy with PI.[6]

There are no monotherapy trials that specifically analyze the change from DRV/r to darunavir with cobicistat (DRV/c); however, there is evidence that in combination therapies, the change is safe when control of the viral load (VL) is maintained.[7–9] Furthermore, the DRV active ingredient is formulated with the enhancer cobicistat DRV/c in a single tablet, unlike DRV/r, which is administered in 2 separate tablets. These 2 reasons, together with other factors, such as fewer interactions of cobicistat in relation to ritonavir and the lower treatment cost, have meant that in Spain, nearly all patients undergoing monotherapy receive DRV/c. Other treatments in monotherapy were ritonavir-boosted lopinavir (LPV/r) and the DRV/r, although there is currently a residual proportion of patients in monotherapy with ritonavir as an enhancer.

The aim of the study was to evaluate the reasons for changing to monotherapy with PI, together with the proportion and reasons for the clinics interrupting the treatment, in all patients treated at some point with DRV/c. Furthermore, the clinical variables that influence the possible treatment failures were analyzed, both in those patients who have failed and in those who have continued treatment in monotherapy.

2. Methods

An observational retrospective study was undertaken in a tertiary hospital, and covers the data gathered between the years 1990 and 2022.

The study population included all adult patients with HIV infection undergoing treatment with DRV/c (800 mg/150 mg), from December 2014, when the drug was authorized in Spain.

The inclusion criteria were having received treatment with DRV/c in monotherapy and starting treatment with ART between 1990 and 2022.

The grounds for exclusion were not collecting their antiretroviral medication in the study hospital, incomplete medical history, not having an electronic record of ART, and not having an electronic medical history.

The demographic variables collected were gender, route of transmission (injecting drug user, men who have sex with men, recipients of hemoderivatives, maternal-fetal transmission, heterosexual relationships or unknown cause), coinfection with hepatitis c virus, age at the start of monotherapy, and duration of ART treatment. The detectable VL was ≥ 20 copies, due to it being the limit of detection of our center's analytical technique, and a VL ≥ 200 copies was defined as a *blip* with clinical significance (all patients with a *blip* or detectable VL in 2 consecutive samples would be considered VF), as per the GeSIDA guidelines. The number of previous treatments and the reason for changing to monotherapy were also recorded, in addition to previous treatments in monotherapy and duration; adherence, initial VL, VL 12 weeks into treatment, VL at the end of monotherapy, initial cluster of differentiation 4 lymphocyte (CD4), CD4 12 weeks into treatment; CD4 at the end of monotherapy; number of *blips*; and the reason for abandoning monotherapy.

Lastly, the same VL and CD4 count variables were collected following discontinuation of monotherapy.

Adherence was decided according to the dispensing record following simplification of the treatment and the interruption of monotherapy: very good [> 99%]; good [98.9%–95%]; normal [94.9%–80%]; and poor [< 80%]. A 30% increase or decrease in relation to the previous count was considered a variation of CD4. All the variables were collected consulting the Medical History and the dispensing program of the outpatient pharmaceutical care unit.

In the statistical analysis, the quantitative variables were expressed as mean and standard deviation (SD), and the categorical variables, as frequencies and percentages. The comparison of means was performed using the *Student's t* test. A *P* value of < .05 was considered statistically significant. The statistical analysis was conducted using the software Stata 14.2.

3. Results

3.1. Analysis of treatment with monotherapy

42 patients were included whose demographic variables are described in Table 1. The majority of the patients (41 patients, 98%) previously followed a monotherapy regimen different to DRV/c (28 patients [67%] started monotherapy with DRV/r; 13 patients [31%] with LPV/r), and 22 patients (52%) had more than 3 different regimens of ART before changing to monotherapy (mean: 6 [SD: 4]). In July 2022, the mean duration of monotherapy was 8 years and 4 months (SD: 3).

Table 2 shows the results relating to the evolution of VL, CD4 and treatment adherence. During monitoring, 29 patients (69%) showed very good/good adherence. Of the 12 patients (29%) with normal or poor adherence, 5 (12%) had virological rebound at some point (3 patients had detectable VL and 2 had *blips* above 200 copies), meeting VF criteria, and 10 of the patients with normal/poor adherence (77% of the patients) stopped monotherapy.

A total of 27 patients (64%), 20 males and 7 females, stopped treatment with monotherapy, with a mean age of 47 years (SD: 10). In this subgroup, the mean duration of monotherapy was 7 years and 5 months (SD: 3), and the time from the end of the treatment to analysis was 3 years and 1 month (SD: 2). 18 patients (67%) changed to triple therapy, and the remaining patients, to double combination therapy,

Table 1

Patient characteristics.

	N = 42
Mean age at the start of monotherapy, yr (SD)	46 (9)
Female, n (%)	11 (26)
Route of transmission, n (%)	
Unknown	15 (36)
Heterosexual relationships	10 (24)
MSM	10 (24)
IDU	5 (12)
Vertical	1 (2)
Hemoderivative transfusion	1 (2)
HCV-coinfected patients, n (%)	20 (48)
Treatment prior to monotherapy, n (%)	
Double therapy	4 (10)
Triple therapy	37 (88)
Without ART	1 (2)
PI as part of ART	34 (81)
Reason for changing to monotherapy, n (%)	
Simplification	34 (81)
Adverse reactions	6 (14)
Interaction with HCV treatment	2 (5)

ART = antiretroviral therapy, HCV = hepatitis C virus, IDU = injecting drug users, MSM = men who have sex with men, PI = boosted protease inhibitor, SD = standard deviation.

maintaining DRV as part of the treatment in 14 patients (52%), and in the other 13 patients (48%), it was replaced with an INSTI.

The evolution of the patients after discontinuing monotherapy is summarized in Table 3. Prior to the discontinuation of monotherapy, only 7 patients (26%) had a detectable VL (≥ 20 copies/ml), although only 1 patient had persistent detectable VL in the period meeting VF criteria. Following the change to ART, all the patients had undetectable VL. At the time of analysis, 26 patients (96%) had undetectable VL, and in 1 patient, a viremia of 44 copies/mL was recorded. No patients had a reduced CD4/μL count at the time of analysis. The mean adherence in the subgroup during monotherapy and after termination of the monotherapy was 95.1% and 94.8%, respectively, with no significant statistical differences ($P = .9133$). At the end of the trial, 7 patients had treatment with more than 1 daily tablet and 20 patients, with a single tablet, with an average adherence of 91% and 96%, respectively. In total, 15 patients (36%) were still undergoing monotherapy at the time of the analysis and 2 died during the study period.

The most usual combination of drugs following discontinuation was a single tablet of cobicistat-boosted darunavir, with emtricitabine and tenofovir alafenamide and therapy with DRV/c + 3TC, as in Table 4. At the time of the study (July 2022), most patients had changed to triple combination therapy with bictegravir, emtricitabine, and tenofovir alafenamide or DTG/3TC double combination therapy, as seen in Table 5.

4. Discussion

The complexity of the patients due to the increase in comorbidities and polypharmacy with the resulting implications (associated at times to low adherence),[10] has forced HIV specialists to explore alternatives to ART in recent decades. Our cohort is a clear example of these kinds of complex patients, as nearly half of the study population are hepatitis c virus-coinfected patients and 12% of the patients are injecting drug user (Table 1). Some of the patients had received treatments in monotherapy since the start of the decade of 2000, when simple dosages (a tablet with multiple active ingredients) were not part of the therapeutic arsenal.

On the other hand, monotherapy with PI arises at a time in which ART presented multiple AEs, such as lipodystrophy, deterioration of renal function, and neurocognitive toxicity,[11,12] which adds an additional obstacle in the patients' continuity of the treatment. In our study, only 7 (17%) of the patients failed monotherapy with PI due to AEs (Table 3 and 4), which confirms the finding by Cameron et al whereby monotherapy with PI reduced the incidence of AEs in relation to combinations with a nucleoside analog reverse transcriptase inhibitor (NRTI), with 5% on LPV/r in monotherapy.[11] It should be added that in the study MONOI ANRS 136, 11% of the patients with DRV/r-based monotherapy presented serious AEs in week 96, which is a similar result to that of our patients.[12]

Although the long-term retrospective design of our study does not allow us to reliably compare the results with other patient cohorts with PI in monotherapy, we can say that our results are similar to others in terms of the incidence of serious AEs.[11,13]

The chronicity of the treatments together with their potential AEs may explain the 9 patients with poor/normal adherence, which has already been demonstrated by other authors such as El Bouzidi et al in their 10-year retrospective study that included 95 patients treated with PI in monotherapy with 21% of abandonment after 4 years.[14] In our study, 1 of the main reasons for discontinuing monotherapy was poor adherence (14% of the total patients in monotherapy), which confirms the difficulty of treating this specific patient profile.

That said, at the end of the study 1 to 3rd of the patients continued ART in monotherapy, which shows that it is still a

Table 2

Variables during treatment with monotherapy.

Variables	N = 42
Detectable viral load, n (%)	
Prior to monotherapy	4 (10)
12 w after changing to monotherapy	5 (12)
Last analysis during monotherapy	9 (21)
Patients with blips during monotherapy	5 (12)
Lymphocyte population, CD4/μL (SD)	
Prior to monotherapy	700 (228)
12 w after changing to monotherapy	642 (226)
Last analysis during monotherapy	845 (290)
Patients with > 30% increase of CD4, n (%)	
12 w after changing to monotherapy	4 (10)
Last analysis during monotherapy	16 (38)
Patients with > 30% decrease of CD4, n (%)	
12 w after changing to monotherapy	5 (12)
Last analysis during monotherapy	0 (0)
Adherence to monotherapy, n (%)	
Very good (> 99%)	18 (43)
Good (98.9%–95%)	11 (26)
Normal (94.9%–80%)	12 (29)
Poor (< 80%)	1 (2)

CD4 = cluster of differentiation 4 lymphocyte, SD = standard deviation.

Table 3

Variables following discontinuation of the treatment with monotherapy.

Variables	N = 27
Detectable viral load, n (%)	
Prior to discontinuation	7 (26)
12 w after changing to double/triple combination therapy	1 (4)
Last analysis	1 (4)
Patients with *blips*	0 (0)
Lymphocyte population, CD4/μL (SD)	
Prior to discontinuation	826 (310)
12 w after changing to double/triple combination therapy	827 (345)
Last analysis	910 (345)
Patients with > 30% increase of CD4, n (%)	
12 w after changing to double/triple combination therapy	4 (15)
Last analysis during discontinuation	5 (19)
Patients with > 30% decrease of CD4, n (%)	
12 w after changing to double/triple combination therapy	3 (11)
Last analysis during discontinuation	0 (0)
Adherence after changing to double/triple combination therapy, n (%)	
Very good (> 99%)	13 (48)
Good (98.9%–95%)	5 (19)
Normal (94.9%–80%)	7 (26)
Poor (< 80%)	2 (7)
Reason for discontinuation, n (%)	
Physician's decision without specifying	8 (30)
Adverse reaction	7 (26)
Poor adherence	6 (22)
Virological failure	3 (11)
Other reasons	3 (11)
ART after changing to double/triple combination therapy, n (%)	
Double therapy	9 (33)
PI	6 (22)
INSTI	3 (11)
Triple therapy	18 (67)
PI	8 (30)
INSTI	10 (37)
Single daily tablet	17 (63)
> 1 daily tablet	10 (37)

ART = antiretroviral therapy, CD4 = cluster of differentiation 4 lymphocyte, INSTI = integrase strand transfer inhibitor, PI = boosted protease inhibitor, SD = standard deviation.

Table 4

Number of patients according to antiretroviral therapy following discontinuation and reason for discontinuation.

	Reason				
ART	**Medical decision**	**ADR**	**Poor adherence**	**Virological failure**	**Other**
DRV/COBI/FTC/TAF	**3**		**1**	**1**	
BIC/TAF/FTC	**1**	**2**			
ABC/DTG/3TC		**1**		**1**	**1**
EVG/COBI/FTC/TAF		**1**	**1**		
DTG + FTC/TAF		**1**			**1**
DRV/c + ABC/3TC				**1**	
DRV/c + FTC/TAF		**1**	**1**		
DRV/c + 3TC	**1**		**3**		**1**
DTG/3TC	**2**	**1**			
DRV/c + RPV	**1**				

ABC/DTG/3TC = abacavir, dolutegravir and lamivudine, ADR = Adverse Drug Reaction, ART = antiretroviral therapy, BIC/TAF/FTC = bictegravir, tenofovir alafenamide and emtricitabine, DRV/c+3TC = darunavir boosted with cobicistat and lamivudine, DRV/c+ABC/3TC = cobicistat-boosted darunavir, abacavir and lamivudine, DRV/c+FTC/TAF = cobicistat-boosted darunavir, emtricitabine and tenofovir alafenamide, DRV/c+RPV = cobicistat-boosted darunavir and rilpivirina, DRV/COBI/FTC/TAF = cobicistat-boosted darunavir, emtricitabine and tenofovir alafenamide, DTG/3TC = dolutegravir and lamivudine, DTG+FTC/TAF = dolutegravir, emtricitabine and tenofovir alafenamide, EVG/COBI/FTC/TAF = cobicistat-boosted elvitegravir, emtricitabine and tenofovir alafenamide.

Table 5

Treatment following discontinuation versus treatment at end of study.

		End								
		DRV/COBI/ FTC/TAF	**BIC/TAF/ FTC**	**ABC/ DTG/3TC**	**EVG/COBI/ FTC/TAF**	**DTG + FTC/ TAF**	**DRV/c + ABC/3TC**	**DRV/c + FTC/ TAF**	**DRV/c + 3TC**	**DTG/3TC**	**DRV/c + RPV**
Prior	DRV/COBI/FTC/ TAF	**2**	**2**							**1**	
	BIC/TAF/FTC		**3**								
	ABC/DTG/3TC				**1**					**2**	
	EVG/COBI/FTC/ TAF		**1**		**1**						
	DTG + FTC/TAF		**1**			**1**					
	DRV/c + ABC/3TC				**1**						
	DRV/c + FTC/TAF							**1**	**1**		
	DRV/c + 3TC								**4**	**1**	
	DTG/3TC									**3**	
	DRV/c + RPV		**1**								

ABC/DTG/3TC = abacavir, dolutegravir and lamivudine, BIC/TAF/FTC = bictegravir, tenofovir alafenamide and emtricitabine, DRV/c+3TC: darunavir boosted with cobicistat and lamivudine, DRV/c+ABC/3TC = cobicistat-boosted darunavir, abacavir and lamivudine, DRV/c+FTC/TAF = cobicistat-boosted darunavir, emtricitabine and tenofovir alafenamide, DRV/c+RPV = cobicistat-boosted darunavir and rilpivirina, DRV/COBI/FTC/TAF = cobicistat-boosted darunavir, emtricitabine and tenofovir alafenamide, DTG/3TC = dolutegravir and lamivudine, DTG+FTC/TAF = dolutegravir, emtricitabine and tenofovir alafenamide, EVG/COBI/FTC/TAF = cobicistat-boosted elvitegravir, emtricitabine and tenofovir alafenamide.

viable alternative in some selected patients; however, the reason for this is not the improvement in adherence on simplifying the taking of antiretrovirals, but rather, above all, the avoidance of continued exposure to multiple active ingredients and the contraindication of NRTI, as well as the reluctance of the patients to change treatment.[15] This would explain the reason for prescribing double combination therapy to many of our patients with discontinued monotherapy, despite the change to triple therapy being recommended in patients with poor adherence or VF.[1]

In most patients the CD4 lymphocyte count following the start of monotherapy increased, although in the last analysis, 21% of the patients with monotherapy had detectable VL. Comparing the group that supports the ART program with monotherapy with the patients who stopped the treatment, there is a lower proportion of patients with detectable VL in patients with double or triple therapy than in those patients with monotherapy, as shown in Table 3. The percentage of patients with virological failure in the retrospective study by El Bouzidi et al was 64%, which is significantly > our result of 21%.[14] The main reason for this may be the different definition of virological failure (detectable VL vs detectable VL in 2 consecutive samples or *blip* above 200 copies/μL), as shown in Table 2. At the end of the analysis of the subgroup following discontinuation of monotherapy (mean follow-up of 3 years and 1 month), the percentage of patients with detectable VL was just 4%, as shown in Table 3, which are similar to the results of other studies.[16–18] This confirms that, although PIs are powerful drugs, they are less effective for controlling HIV when administered in monotherapy.

Lastly, we must point out the limitations of this study, whereby its retrospective nature complicates the collection of relevant data. Furthermore, we must add that, although this study includes nearly all those patients in monotherapy during the study period (mainly based on DRV/c, since DRV/r or LPV/r are of residual use), the sample size was limited, which makes obtaining results with statistical power difficult and barely generalizable.

In conclusion, the antiretroviral therapy recommendations in the GeSIDA guidelines recommend against exposing the patient to functional monotherapy with a single drug due to the elevated risk of VF and onset of resistance to said single drug. Following the analysis of the results of our study, we can confirm that DRV/c in monotherapy is a treatment with a high discontinuation rate, which does not improve adherence to ART and that currently presents unacceptable rates of detectable

viremia. Monotherapy is not an effective strategy in the medium and long term due to factors such as the lack of adherence or VF. For this reason, patients undergoing monotherapy require close monitoring.

Author contributions

Conceptualization: Antonio Solana-Altabella, Emilio Monte-Boquet, Pablo Pérez-Huertas, Maria Jesús Cuéllar-Monreal.
Data curation: Antonio Solana-Altabella, Pablo Pérez-Huertas.
Formal analysis: Antonio Solana-Altabella, Pablo Pérez-Huertas.
Funding acquisition: Antonio Solana-Altabella, José Luis Poveda-Andrés.
Investigation: Antonio Solana-Altabella, Emilio Monte-Boquet.
Methodology: Antonio Solana-Altabella, Emilio Monte-Boquet.
Project administration: Antonio Solana-Altabella, José Luis Poveda-Andrés.
Resources: Antonio Solana-Altabella.
Software: Antonio Solana-Altabella.
Supervision: Antonio Solana-Altabella, Emilio Monte-Boquet, Marta Montero, Maria Jesús Cuéllar-Monreal, Miguel Salavert, José Luis Poveda-Andrés.
Validation: Antonio Solana-Altabella, Emilio Monte-Boquet, Marta Montero, Maria Jesús Cuéllar-Monreal, Miguel Salavert, José Luis Poveda-Andrés.
Visualization: Antonio Solana-Altabella, Emilio Monte-Boquet, Marta Montero, Maria Jesús Cuéllar-Monreal.
Writing – original draft: Antonio Solana-Altabella, Emilio Monte-Boquet, Marta Montero, Maria Jesús Cuéllar-Monreal.
Writing – review & editing: Antonio Solana-Altabella, Emilio Monte-Boquet, Marta Montero, Pablo Pérez-Huertas, Maria Jesús Cuéllar-Monreal, Miguel Salavert, José Luis Poveda-Andrés.

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