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Factors associated with the number of drugs in darunavir/cobicistat regimens

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Background: Darunavir/cobicistat can be used as mono, dual, triple or more than triple therapy.

Objectives: To assess factors associated with the number of drugs in darunavir/cobicistat regimens.

Methods: A nationwide retrospective cohort study of consecutive HIV-infected patients initiating darunavir/cobicistat in Spain from July 2015 to May 2017. Baseline characteristics, efficacy and safety at 48 weeks were compared according to the number of drugs used.

Results: There were 761 patients (75% men, 98% were antiretroviral-experienced, 32% had prior AIDS, 84% had HIV RNA <50 copies/mL and 88% had ≥200 CD4 cells/mm^3) who initiated darunavir/cobicistat as mono (*n*=308, 40%), dual (*n*=173, 23%), triple (*n*=253, 33%) or four-drug (*n*=27, 4%) therapy. Relative to monotherapy, triple therapy was more common in men aged <50 years, with prior AIDS and darunavir plus ritonavir use, and with CD4 cells <200/mm^3 and with detectable viral load at initiation of darunavir/cobicistat; dual therapy was more common with previous intravenous drug use, detectable viral load at initiation of darunavir/cobicistat and no prior darunavir plus ritonavir; and four-drug therapy was more common with prior AIDS and detectable viral load at initiation of darunavir/cobicistat. Monotherapy and dual therapy showed a trend to better virological responses than triple therapy. CD4 responses and adverse effects did not differ among regimens.

Discussion: Darunavir/cobicistat use in Spain has been tailored according to clinical characteristics of HIV-infected patients. Monotherapy and dual therapy have been common and preferentially addressed to older patients with a better HIV status, suggesting that health issues other than HIV infection may have been strong determinants of its prescription.

Introduction

The emergence of PIs into clinical practice changed the natural history of HIV infection in the mid-1990s, but enthusiasm was soon tempered by the limited bioavailability and common severe toxicity of the compounds that were available initially.[1] The use of boosting agents improved pharmacokinetics, allowing once-daily dosing, and new, safer and better-tolerated compounds progressively replaced older, more toxic, ones.[2] Out of many PIs licensed, darunavir currently stands as the most widely recommended and commonly used because of its potency and tolerability.[3–5] Initially dosed at 600 mg in combination with ritonavir 100 mg twice daily for salvage therapy, darunavir became later recommended at a dose of 800 mg plus ritonavir 100 mg daily for the majority of patients.[2] Cobicistat was developed as a boosting agent later than low-dose ritonavir. Cobicistat is better tolerated, has no cytochrome P450 (CYP) 3A inhibitor inducer or antiretroviral effects,

and is co-formulated with darunavir.[6] For these reasons, when available, cobicistat-boosted darunavir formulations have been increasingly preferred over ritonavir-boosted darunavir formulations.

Major guidelines have long established triple regimens consisting of two NRTIs plus a third drug as the gold standard of antiretroviral therapy.[3–5] Antiretroviral drugs have improved over time, becoming more effective, simpler and better tolerated. However, for some patients, standard triple antiretroviral regimens may still be challenging because of antiretroviral-related adverse effects, negative impact on comorbidities, risk of interactions, archived resistance, or other reasons, therefore justifying the need for an individualized therapeutic approach with other than triple regimens.[7] Ritonavir-boosted darunavir has been used not only in standard triple regimens but also in monotherapy,[8,9] dual therapy[10] and salvage therapy containing more than three drugs,[11] thus making it a versatile option for individualized therapy. With few exceptions, cobicistat-boosted darunavir can be used in a way similar to ritonavir-boosted darunavir but real-life data are scarce. We aimed to determine the characteristics of darunavir/cobicistat use in HIV-infected adults in Spain. We hypothesized that the use of darunavir/cobicistat as mono, dual, triple or more than triple therapy would be associated with specific characteristics of HIV-infected patients.

Patients and methods

Study population and design

We designed a nationwide retrospective cohort study of consecutive HIV-infected adults (aged ≥18 years) treated for the first time with at least one dose of any regimen containing darunavir/cobicistat from the beginning of July 2015 until the end of May 2017. Twenty-one hospitals across Spain participated in the study under the coordination of the Spanish AIDS Study Group (GeSIDA). For the purpose of this study, the database was closed by the end of November 2017, allowing a potential follow-up of at least 24 weeks. Baseline was defined as the date of darunavir/cobicistat initiation. The following baseline variables were obtained from medical records whenever available: age, gender, ethnicity, date of HIV diagnosis, CD4 cell count, plasma HIV RNA, any prior AIDS-defining event, presumed HIV transmission route, hepatitis C coinfection (defined by a positive serology), prior hepatitis C treatment, any prior antiretroviral therapy, prior therapy including darunavir plus ritonavir, and reason for starting darunavir/cobicistat-containing therapy categorized as any of the following: being antiretroviral naive, treatment simplification, toxicity/intolerance, drug–drug interactions, virological failure, other, or non-available. Besides baseline data, additional data on efficacy and safety at 12, 24 and 48 (when available) weeks with a pre-defined window of ±6 weeks were also collected. Ethics approval was obtained and all eligible patients provided signed informed consent. Since signed consent was required for the study, it is possible that some potential users of darunavir/cobicistat were no longer treated in the participating centres or not alive during the inclusion period and therefore were not represented. The study is registered at ClinicalTrials.gov NCT03042390.

Outcomes and statistical analyses

By the time of the study design, there were roughly 7000 patients taking darunavir/cobicistat in Spain according to Janssen Spain estimates. Twenty-one hospitals throughout Spain were asked to and agreed to participate in the study. In these 21 hospitals, 3750 patients met the criteria for participating in the study. A sample of 10% of the total population was deemed representative for the purpose of the study. This sample was finally established at 761 patients. We assessed major characteristics of interest in these 761 patients and the remaining 2739 patients meeting inclusion criteria in the 21 participating centres but not selected for the study, and we confirmed that there were no statistical differences in them (data not shown).

Baseline characteristics and efficacy and safety at 24 and 48 weeks were compared according to the number of antiretroviral drugs used in the regimen by χ^2 or Fisher's exact tests for categorical variables or Student's *t*-test or Wilcoxon tests for continuous variables. Multinomial regression was used to identify factors associated with the regimen used; after a preliminary exploratory analysis, monotherapy was arbitrarily chosen as the reference for comparisons because it turned out to be the most common darunavir/cobicistat regimen used in Spain. Linear or logistic regression was used for comparison of changes in CD4 cells and rates of viral suppression among darunavir/cobicistat regimens because these variables were collected only at certain timepoints for the purpose of the study (for instance, if a participant had several viral load measurements from week 12 to week 24, only the measurement in the week 24 window was collected). Cumulative incidence of darunavir/cobicistat discontinuation and adverse events were compared with Poisson regression. All statistical analyses were performed using Stata software (version 15.0; Stata Corporation, College Station, TX, USA). The significance level considered was 0.05.

Results

Baseline characteristics

There were 761 patients included in this study (Table 1). Mean (SD) age was 49 (10) years. Three out of every four patients were men and >90% were Caucasian. Roughly one out of three patients had any AIDS-defining condition. Eighty-eight percent of them had CD4 counts ≥200 cells/mm^3, with a mean (SD) CD4 cell count at baseline of 661 (333) cells/mm^3, and 84% had plasma HIV RNA <50 copies/mL. Hepatitis C coinfection was present in one-third of patients, of whom slightly less than half had received anti-hepatitis C treatment. The majority of patients had received prior ritonavir-boosted darunavir-containing therapy (n=610, 80%), while only a minority were antiretroviral naive (n=12, 2%). The most common reason for starting darunavir/cobicistat was treatment simplification (n=618, 81%). Table S1 (available as Supplementary data at *JAC* Online) shows antiretroviral regimens prior to darunavir/cobicistat use and number of patients per regimen.

Baseline factors associated with regimen

Of the 761 patients included, 308 (40%) received darunavir/cobicistat as monotherapy, 173 (23%) as dual therapy, 253 (33%) as triple therapy and 27 (4%) as four-drug therapy (Table 1). Table 2 shows baseline factors associated with regimen. Relative to patients on monotherapy, patients on triple therapy more commonly had mean age <50 years, prior AIDS and darunavir plus ritonavir use, and CD4 counts <200 cells/mm^3 and detectable viral load at initiation of darunavir/cobicistat. Relative to patients on monotherapy, patients on dual therapy had more commonly acquired HIV infection through intravenous drug use, had no prior darunavir plus ritonavir use and had detectable viral load at initiation of darunavir/cobicistat. Relative to patients on monotherapy, patients on four-drug therapy were not co-infected with hepatitis C, and more commonly had prior AIDS and detectable viral load at initiation of darunavir/cobicistat.

Table 1. Baseline characteristics

	Regimen					
	triple (*n*=253, 33%)	mono (*n*=308, 40%)	dual (*n*=173, 23%)	4-drug (*n*=27, 4%)	Total (*n*=761)	*P* value
Age, years	46 (10)	50 (10)	50 (9)	49 (11)	49 (10)	<0.001
Men, *n* (%)	201 (79)	220 (71)	124 (72)	23 (85)	568 (75)	0.067
Caucasian, *n* (%)	216 (85)	297 (96)	160 (92)	21 (78)	694 (91)	<0.001
Time from HIV diagnosis, years	14 (9)	17 (8)	18 (8)	17 (9)	16 (9)	<0.001
Nadir CD4 count, cells/mm^3	202 (179)	251 (179)	227 (183)	220 (228)	228 (183)	<0.001
Prior AIDS, *n* (%)	88 (35)	73 (24)	69 (40)	17 (63)	247 (32)	<0.001
HIV transmission, *n* (%)						0.013
MSM	81 (32)	120 (39)	40 (23)	11 (41)	252 (33)	
IVDU	77 (30)	79 (26)	71 (41)	10 (37)	237 (31)	
heterosexual	72 (28)	86 (28)	49 (28)	3 (11)	210 (28)	
other/NA	23 (9)	23 (8)	13 (7)	3 (11)	62 (8)	
CD4 count ≥200 cells/mm^3, *n* (%)	216 (85)	271 (88)	159 (92)	25 (93)	671 (88)	<0.001
CD4 count, cells/mm^3	557 (323)	745 (306)	699 (341)	530 (344)	662 (333)	<0.001
Viral load <50 copies/mL, *n* (%)	194 (77)	283 (92)	145 (84)	17 (63)	639 (84)	<0.001
Plasma log HIV RNA, copies/mL	1.85 (1.10)	1.43 (0.34)	1.59 (0.70)	2.17 (1.35)	1.63 (0.82)	0.019
HCV coinfection, *n* (%)	90 (36)	88 (29)	75 (43)	6 (22)	259 (34)	0.015
Hepatitis C successfully treated, *n* (%)	42 (17)	31 (10)	38 (22)	5 (19)	116 (15)	0.005
Previous antiretroviral therapy, *n* (%)						<0.001
none	11 (4)	0 (0)	0 (0)	1 (4)	12 (2)	
RTV-boosted darunavir	211 (83)	255 (83)	123 (71)	21 (78)	610 (80)	
no RTV-boosted darunavir	31 (12)	53 (17)	50 (29)	5 (19)	139 (18)	
Reason for starting darunavir/cobicistat, *n* (%)						<0.001
naive	9 (4)	0 (0)	0 (0)	1 (4)	10 (1)	
simplification	192 (76)	269 (87)	137 (79)	20 (74)	618 (81)	
toxicity/intolerance	11 (4)	21 (7)	17 (10)	0 (0)	49 (6)	
interactions	1 (0)	1 (0)	2 (1)	2 (7)	6 (1)	
virological failure	15 (6)	1 (0)	7 (4)	2 (7)	25 (3)	
other	16 (6)	6 (2)	6 (3)	1 (4)	29 (4)	
NA	9 (4)	10 (3)	4 (2)	1 (4)	24 (3)	

Data are mean (SD) unless otherwise stated.
NA, not available; RTV, ritonavir.

Virological and immunological responses at 24 and 48 weeks

Virological responses are shown in Table 3. Overall, 89% of patients had plasma HIV RNA <50 copies/mL at both 24 (*n*=652) and 48 (*n*=495) weeks. Monotherapy (93% at 24 weeks and 92% at 48 weeks) and dual therapy (90% at 24 weeks and 93% at 48 weeks) showed a trend to better virological responses relative to triple therapy (85% at 24 weeks and 83% at 48 weeks). Immunological responses are shown in Table 4. Overall, there were median increases of 18 and 13 CD4 cells/mm^3 at 24 (*n*=579) and 48 (*n*=451) weeks, respectively. There were no significant differences in immunological responses among darunavir/cobicistat regimens.

Tolerability

Overall, out of 761 patients with a potential follow-up of 24 weeks, 94 (12.4%) had darunavir/cobicistat therapy discontinued and 3 (0.4%) died (Table 5). Rates of darunavir/cobicistat discontinuation at 24 weeks were lower for monotherapy (9.4%) or dual therapy (11.5%) as compared with triple (15.0%) or four-drug (25.9%) therapies. Overall, the most common reasons for change were toxicity/intolerance (*n*=37, 39% of the discontinuations) or interactions (*n*=21, 22% of the discontinuations). The rates of any adverse event, any adverse event of grade 2–4 or any discontinuation due to intolerance/toxicity did not differ among darunavir/cobicistat regimens (Table 6).

Discussion

This paper reports one of the largest cohort studies of HIV-infected patients treated with darunavir/cobicistat. It reveals important real-life data on the use of this PI in Spain. Patients in the cohort had similar characteristics to those reported for the general HIV adult population in Spain,[12] except that they were slightly older. A large proportion of patients (81%) had switched from darunavir plus ritonavir with the primary aim of treatment simplification. In contrast with ritonavir boosting, cobicistat and darunavir have

Table 2. Baseline factors associated with regimen

	OR (95% CI)		
	triple vs mono	dual vs mono	4-drug vs mono
Age			
<50 years	1	1	1
≥50 years	0.504 (0.347–0.733)	1.234 (0.824–1.846)	0.766 (0.323–1.815)
Gender			
men	1	1	1
women	0.495 (0.301–0.815)	0.727 (0.440–1.201)	0.584 (0.160–2.130)
Prior AIDS			
no	1	1	1
yes	1.745 (1.169–2.603)	1.933 (1.270–2.943)	5.644 (2.325–13.697)
HIV transmission route			
MSM	1	1	1
IVDU	1.493 (0.790–2.823)	2.084 (1.064–4.084)	3.139 (0.904–10.894)
heterosexual	1.588 (0.932–2.707)	1.856 (1.021–3.374)	0.466 (0.104–2.093)
other/not available	1.668 (0.557–4.996)	0.770 (0.151–3.925)	NA
CD4 count, cells/mm^3			
<200	1	1	1
≥200	0.256 (0.097–0.671)	0.516 (0.171–1.558)	1.102 (0.096–12.713)
Plasma HIV RNA (copies/mL)			
<50	1	1	1
50–100000	3.097 (1.642–5.841)	2.207 (1.112–4.378)	7.034 (2.419–20.459)
≥100000	NA	NA	NA
HCV coinfection			
no	1	1	1
yes	1.225 (0.709–2.116)	1.283 (0.728–2.262)	0.256 (0.073–0.898)
Previous ART			
no darunavir/cobicistat	1	1	1
darunavir/cobicistat	1.726 (1.015–2.934)	0.511 (0.319–0.819)	1.275 (0.415–3.920)
naive	NA	NA	NA

For model convergence reasons, monotherapy has been selected as reference.
NA, not applicable.

Table 3. Virological response at 24 (P=0.393) and 48 (P=0.298) weeks

	24 weeks			48 weeks		
Regimen	patients available	<50 copies/mL, *n* (%)	adjusted[a] OR (95% CI)	patients available	<50 copies/mL, *n* (%)	adjusted[a] OR (95% CI)
Triple	215	182 (85)	1	162	134 (83)	1
Mono	269	249 (93)	1.8 (0.8–3.8)	219	201 (92)	1.6 (0.8–3.2)
Dual	144	129 (90)	1.2 (0.6–2.6)	98	91 (93)	2.2 (0.8–6.0)
4-Drug	24	19 (79)	1.0 (0.3–3.1)	17	15 (88)	1.9 (0.5–8.1)
Total	652	579 (89)		495	441 (89)	

[a]Adjusted by centre, baseline CD4 and other baseline variables (gender, AIDS, HCV coinfection, age, reason for starting darunavir/cobicistat, prior antiretroviral therapy and plasma HIV RNA).

been always co-formulated, initially as the boosted PI component only and later as a triple regimen together with emtricitabine/tenofovir alafenamide. Besides the appeal of co-formulation, darunavir/cobicistat may be better tolerated than darunavir plus ritonavir.[6,13] Only 2% of the patients included were antiretroviral naive. This may be due at least in part to the fact that Spanish national guidelines recommended triple regimens containing integrase inhibitors for first-line therapy at the time of the study.[14–16] Although boosted darunavir has been the drug preferentially recommended among PIs for antiretroviral-naive HIV-infected

Table 4. Immunological response at 24 (P=0.495) and 48 (P=0.378) weeks

	24 weeks			48 weeks		
Regimen	patients available	ΔCD4, cells/mm^3 (95% CI)	adjusted[a] mean change (95% CI)	patients available	ΔCD4, cells/mm^3 (95% CI)	adjusted[a] mean change (95% CI)
Triple	202	10 (−1 to 37)	0 (reference)	154	27 (−2 to 56)	0 (reference)
Mono	219	20 (−6 to 47)	22.3 (−24.8 to 66.1)	187	−8 (−35 to 18)	−24.9 (−67.5 to 17.7)
Dual	135	22 (−12 to 56)	30.4 (−26.0 to 90.4)	95	32 (−5 to 69)	15.1 (−18.8 to 49.0)
4-Drug	23	38 (−44 to 120)	42.4 (−7.3 to 93.2)	15	3 (−90 to 97)	−13.3 (−89.2 to 62.6)
Total	579	18 (1–34)		451	13 (−4 to 30)	

[a]Adjusted by centre, baseline CD4 and other baseline variables (gender, AIDS, HCV co-infection, age, reason for starting darunavir/cobicistat, prior antiretroviral therapy and plasma HIV RNA).

Table 5. Persistence on darunavir/cobicistat at 24 weeks and reasons for change

	Regimen				
	triple (n=253)	mono (n=308)	dual (n=173)	4-drug (n=27)	Total (n=761)
Darunavir/cobicistat maintained, n (%)	214 (84.6)	278 (90.3)	152 (87.9)	20 (74.1)	664 (87.2)
Darunavir/cobicistat changed, n (%)	38 (15)	29 (9.4)	20 (11.5)	7 (25.9)	94 (12.4)
Reason for change					
toxicity/intolerance	11	18	8	–	37
interactions	9	2	7	2	21
virological failure	1	2	–	1	4
patient's decision	2	1	1	1	5
other	15	6	4	3	28
Death, n (%)	1 (0.4)	1 (0.3)	1 (0.6)	0 (0)	3 (0.4)

Table 6. Rates of any adverse event, any adverse event of grade 2–4 or any discontinuation due to intolerance/toxicity

	Regimen			
Adverse events	triple (n=253)	mono (n=308)	dual (n=173)	4-drug (n=27)
Any adverse event				
rate (per 100 persons/year)	42	62	62	46
IRR (95% CI)	1	1.49 (0.76–2.90)	1.49 (0.79–2.82)	1.11 (0.47–2.60)
Adverse events grade 2–4				
rate (per 100 persons/year)	15	13	13	4
IRR (95% CI)	1	0.85 (0.26–2.80)	0.86 (0.36–2.06)	0.28 (0.04–1.85)
Discontinuation due to intolerance/toxicity				
rate (per 100 persons/year)	5	6	5	0
IRR (95% CI)	1	1.31 (0.46–3.72)	1.09 (0.39–3.08)	–

IRR, incidence risk ratio.

patients in Spain, it was almost exclusively considered for patients with CD4 counts <200 cells/mm^3 or with problems of adherence,[14–16] although its use might increase in the future due to the increasing availability of the single-tablet regimen of darunavir/cobicistat/emtricitabine/tenofovir alafenamide and to the efficacy and safety shown by this co-formulation in the AMBER study.[3,17]

It is remarkable that darunavir/cobicistat was used as a triple therapy in only one-third of patients. The most common use was monotherapy (40%), an option not recommended or used in many settings due to sub-optimal efficacy relative to triple standard therapy.[5] Since several key PI monotherapy studies were initially led by Spanish investigators,[18,19] clinical use of PI monotherapy has not been unusual in Spanish HIV clinics for the

last 15 years.[20,21] Dual therapy is a more recent strategy and therefore less commonly used than PI monotherapy, although it is worth mentioning that major dual therapy studies with boosted PIs, such as OLE,[22] SALT[23] and DUAL,[10] have been done in Spain. In fact, Spanish national guidelines have considered over the years the use of monotherapy and dual therapies containing boosted PIs as potential, though secondary, options to prevent toxicities associated with NRTIs. With the availability of tenofovir alafenamide, darunavir/cobicistat monotherapy or dual therapy may be considered less for clinical use in Spain.

Compared with patients on triple therapy, patients on darunavir/cobicistat monotherapy or dual therapy were older, less commonly men, more commonly Caucasian, had more years after HIV diagnosis, and had higher CD4 cell counts and a more frequently undetectable plasma viral load at baseline. These characteristics suggest that doctors in Spain may have tailored the use of darunavir/cobicistat monotherapy or dual therapy according to health issues other than HIV infection in patients who were HIV suppressed. In accordance with our findings in Spain, a recent EuroSIDA study[24] also suggested that dual regimens have been largely used in Europe for virologically suppressed individuals with higher cumulative exposure to antiretrovirals and comorbidities. Tenofovir disoproxil fumarate and abacavir have been key drugs in the construction of the two-drug NRTI backbone. Tenofovir disoproxil fumarate (kidney and bone) and abacavir (cardiovascular) have been associated with a negative impact on some comorbidities.[4] Because HIV-infected patients at high risk of cardiovascular disease may also have a high risk of chronic kidney disease and vice versa,[25] it is not surprising that darunavir/cobicistat monotherapy initially or dual therapy could later have been reasonable options for HIV-infected patients with any of these comorbidities.

Ninety-four (12%) patients had darunavir/cobicistat discontinued after 48 weeks. This rate is important as this was a retrospective study, without any intervention aimed to promote maintenance of this regimen. Virological failure was uncommon. Virological responses did not differ among darunavir/cobicistat uses. Although PI monotherapy may have a higher risk of virological failure than triple PI-containing therapy,[26] we did not detect it. A potential explanation could be that the population with darunavir/cobicistat monotherapy was more selected than that with triple therapy. Toxicity/intolerance and risk of interactions were among the most common reasons for change, but there were no differences among darunavir/cobicistat regimens regarding any adverse event, adverse events of grade 2–4, or discontinuation due to intolerance/toxicity.

This study had limitations. It reflected the population of HIV-infected adults using darunavir/cobicistat in Spain in the early years after the marketing of this compound. These data may not extend to other countries or settings, or to other time periods in Spain. It was a retrospective, non-controlled study and therefore comparisons of the efficacy of darunavir/cobicistat regimens should be taken with caution. It also had strengths as it included a large population of patients and allowed us to determine the characteristics of darunavir/cobicistat use in HIV-infected adults in Spain, a country in which darunavir/cobicistat has been commonly used as monotherapy or dual therapy.

In summary, darunavir/cobicistat has been a versatile drug in Spain. Doctors have tailored the use of darunavir/cobicistat according to the clinical characteristics of HIV-infected patients. Monotherapy and dual therapy have been common and preferentially addressed to older patients with a better HIV status, suggesting that health issues other than HIV infection may have been the drivers for its prescription.

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Transparency declarations

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Supplementary data

Table S1 is available as Supplementary data at *JAC* Online.

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